Results of a non-specific immunomodulation therapy in chronic heart failure (ACCLAIM trial): a placebo-controlled randomised trial

Guillermo Torre-Amione, Stefan D Anker, Robert C Bourge, Wilson S Colucci, Barry H Greenberg, Per Hildebrandt, Andre Keren, Michael Motro, Lemuel A Moyé, Jan Erik Otterstad, Craig M Pratt, Piotr Ponikowski, Jean Lucien Rouleau, Francois Sestier, Bernhard R Winkelmann, James B Young, for the Advanced Chronic Heart Failure CLinical Assessment of Immune Modulation Therapy Investigators

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Methodist Hospital, Houston, TX, USA (G Torre-Amione MD, C M Pratt MD); **Charité, Campus Virchow-Klinikum, Berlin, Germany** (S D Anker MD); **University of Alabama at Birmingham, Birmingham, AL, USA** (R C Bourge MD); **Boston University School of Medicine, Boston, MA, USA** (W S Colucci MD); **University of California San Diego, Medical Center, San Diego, CA, USA** (B H Greenberg MD); **Frederiksberg Hospital, Frederiksberg, Denmark** (P Hildebrandt MD); **Hadassah University Hospital, Jerusalem, Israel** (A Keren MD); **Chaim Sheba Medical Centre, Tel-Hashomer, Israel** (M Motro MD); **University of Texas Health Science Center, Houston, TX, USA** (L A Moyé MD); **Hospital of Vestfold, Toensberg, Norway** (J E Otterstad MD); **Military Hospital, Wroclaw, Poland** (P Ponikowski MD); **Faculty of Medicine, Université de Montréal, Montreal, QC, Canada** (J L Rouleau MD); **Hôtel Dieu du Centre Hospitalier de L'Université de Montréal, Centre de Recherche, Montreal, QC, Canada** (F Sestier MD); **Kardiologische Gemeinschaftspraxis, Frankfurt, Germany** (B R Winkelmann MD); **and The Cleveland Clinic, Cleveland, OH, USA** (J B Young MD)

Correspondence to: Guillermo Torre-Amione, Medical Director, Heart Transplant Program, Methodist DeBakey Heart Center at The Methodist Hospital, 6550 Fannin, Suite 1901, Houston, TX 77030, USA **gtorre@tmhs.org**

Summary

Background **Evidence suggests that inflammatory mediators contribute to development and progression of chronic heart failure. We therefore tested the hypothesis that immunomodulation might counteract this pathophysiological mechanism in patients.**

Methods **We did a double-blind, placebo-controlled study of a device-based non-specific immunomodulation therapy (IMT) in patients with New York Heart Association (NYHA) functional class II–IV chronic heart failure, left ventricular (LV) systolic dysfunction, and hospitalisation for heart failure or intravenous drug therapy in an outpatient setting within the past 12 months. Patients were randomly assigned to receive IMT (n=1213) or placebo (n=1213) by intragluteal injection on days 1, 2, 14, and every 28 days thereafter. Primary endpoint was the composite of time to death from any cause or first hospitalisation for cardiovascular reasons. The study continued until 828 primary endpoint events had accrued and all study patients had been treated for at least 22 weeks. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00111969.**

Findings **During a mean follow-up of 10·2 months, there were 399 primary events in the IMT group and 429 in the placebo group (hazard ratio 0·92; 95% CI 0·80–1·05; p=0·22). In two prespecified subgroups of patients—those with no history of previous myocardial infarction (n=919) and those with NYHA II heart failure (n=689)—IMT was associated with a 26% (0·74; 0·57–0·95; p=0·02) and a 39% (0·61; 95% CI 0·46–0·80; p=0·0003) reduction in the risk of primary endpoint events, respectively.**

Interpretation **Non-specific immunomodulation may have a role as a potential treatment for a large segment of the heart failure population, which includes patients without a history of myocardial infarction (irrespective of their functional NYHA class) and patients within NYHA class II.**

Introduction

Despite the effectiveness of guideline-based combinations of pharmacological therapies,[1,2] mortality and morbidity associated with chronic heart failure remain unacceptably high. Activation of the immune system in patients with systolic heart failure is associated with increased circulating and tissue concentrations of inflammatory cytokines, activation of complement system, and presence of autoantibodies specific for a range of cardiac antigens.[3] Results from animal models of heart failure show that some inflammatory cytokines and anticardiac antibodies can produce cardiac injury in a form that might lead to cardiac failure. Thus, modulation of this immune response presents an appealing therapeutic target.[4] Despite evidence for the role of inflammation in the progression of heart failure, no specific therapy addressing this patho-physiological mechanism exists, and interventions targeting a specific inflammatory cytokine—such as tumour necrosis factor (TNF)α—have been disappointing.[5,6] However, a non-specifc approach to modulation of the immune response might lead to clinical benefit in patients with chronic heart failure.[3,4] Such an approach seeks to attenuate the inflammatory response or activate anti-inflammatory pathways, or both. Support for such a strategy has come from a series of small trials that documented benefit from the use of steroids,[7] intravenous immunoglobulin,[8] and immunoadsorption therapy.[9]

Evidence suggests that ex-vivo exposure of a blood sample to controlled oxidative stress initiates apoptosis of leucocytes soon after intramuscular injection of the treated sample. The physiological response of the recipient's immune system to apoptotic cells results in a reduction in inflammatory cytokine production, and upregulation of anti-inflammatory cytokines.[10,11] This combined effect on the immune system might be especially beneficial to patients with chronic heart failure, since the inflammation associated with it shows an imbalance of two opposing sides of the cytokine network.[12] Results from preclinical studies using apoptotic cells as the immunomodulatory stimulus have shown reductions in inflammation and in production of inflammatory mediators,[13–15] increases in anti-inflammatory cytokine expression, and decreased cell death.[15]

In a pilot study of 73 patients with moderate to severe heart failure, ex-vivo exposure of autologous blood to controlled oxidative stress and subsequent intramuscular

Panel: List of primary and secondary endpoints

Primary
- Death from any cause or cardiovascular hospitalisation

Secondary
- Death or hospitalisation from any cause
- Death from any cause or hospitalisation as a result of worsening heart failure
- Individual components of composite endpoints
- Cardiovascular deaths
- Combined rate of selected cardiovascular outcomes
    - Sudden cardiac death
    - Non-fatal myocardial infarction
    - Non-fatal ischaemic stroke
    - Unstable angina
    - Coronary revascularisation
- Clinical composite score
- Total days alive and out of hospital
- Change in QTc
- Change in New York Heart Association functional classification
- Change in health-related quality of life
- Cardiovascular-related health-care use
- Change in C-reactive protein concentrations

administration resulted in a reduction of both all-cause mortality and hospital admissions.[16] We tested the hypothesis that this novel immunomodulation strategy would confer a mortality and morbidity benefit in patients with left ventricular (LV) systolic dysfunction and New York Heart Association (NYHA) functional class II–IV symptoms.

Methods

Patients and study design

Description of the rationale and design of the advanced chronic heart failure clinical assessment of immunomodulation (ACCLAIM) trial have been previously reported.[17] The trial was a prospective, double-blind, randomised, placebo-controlled, parallel group, multicentre trial designed to assess the effects of a non-specific approach to immunomodulation on morbidity and mortality in 2426 patients with NYHA class II–IV chronic heart failure. Recruitment was started after approval by the respective regulatory agencies and independent ethics committees. The institutional review board of each clinical site received, reviewed, and approved the protocol. All patients signed a written consent form, which had also been approved by the board. Patients were 18 years or older, had an LV ejection fraction (LVEF) of not more than 30%, and were receiving optimum heart failure therapy at stable doses for at least 2 weeks before randomisation. Optimum heart failure therapy included an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, with or without a β blocker, digitalis, diuretic, or an aldosterone antagonist. Patients also had been treated in hospital or had received outpatient intravenous therapy (inotrope, brain natriuretic peptide, or diuretic) for their heart failure within the previous 12 months; however, this requirement was subsequently waived for NYHA class III/IV patients with an LVEF of not more than 25% after regulatory and institutional ethics approval for this protocol amendment. Patients were randomly allocated in a one to one manner to receive intramuscular injections of active treatment or equivalent volume of saline according to computer generated code lists. Randomisation was stratified by centre and balanced in random blocks of two, four, or six.

The primary endpoint was the composite of death from any cause or first cardiovascular hospitalisation. Secondary objectives included assessment of the effect of active therapy on clinical status and health-related patient quality of life. All secondary endpoints are listed in the panel. The trial was powered assuming a cumulative rate of all-cause death or cardiovascular hospitalisation of 38% during 15 months in the controls, with a two-sided $\alpha=0\cdot049$ (adjusted for two interim analyses) and 90% power. On the basis of these assumptions, 2016 patients were needed to show an 18% reduction of events in the active group.[18] Deaths and hospitalisations were adjudicated by a central endpoint committee, which was unaware of treatment allocation. A data and safety monitoring board assessed all serious adverse events on a continuous basis and completed two interim analyses.

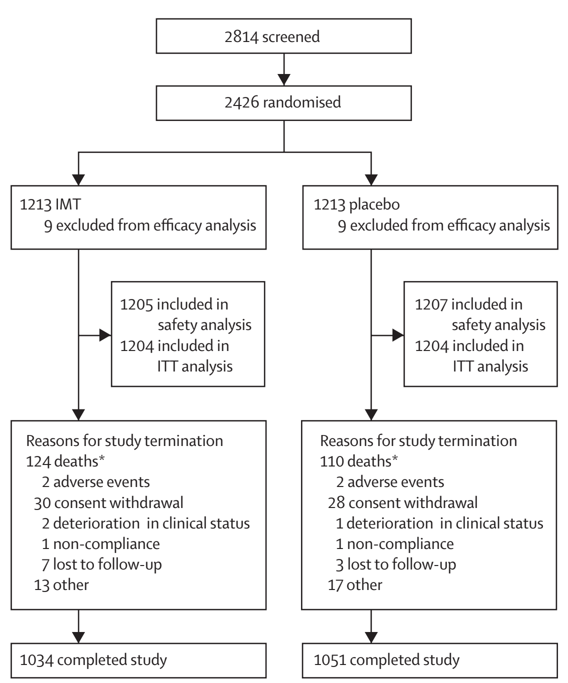

Figure 1: Trial profile
IMT=immunomodulation therapy. ITT=intention to treat. *Includes only deaths that resulted in permanent study discontinuation. 11 additional deaths (four IMT and seven placebo) occurred after patients withdrew for other reason (eg, consent withdrawal).

	IMT (n=1204)	Placebo (n=1204)
Patient characteristics		
Age (years)	64·6 (12·1)	64·0 (11·7)
Men	966 (80%)	966 (80%)
Ethnic origin		
White	1101 (91%)	1104 (92%)
Black	71 (6%)	65 (5%)
Other	32 (3%)	35 (3%)
NYHA functional class		
I	0	1 (0·1%)
II	359 (30%)	329 (27%)
III	797 (66%)	828 (69%)
IV	48 (4%)	46 (4%)
Cause of heart failure		
Ischaemic	818 (68%)	831 (69%)
Non-ischaemic	385 (32%)	873 (31%)
Heart rate* (beats per min)	72 (11)	72 (12)
Systolic blood pressure* (mm Hg)	118 (19)	118 (19)
Diastolic blood pressure* (mm Hg)	70 (12)	70 (11)
C-reactive protein (mg/L), median	3·20 (0·2–49·9)	2·90 (0·2–46·2)
Haemoglobin* (g/L)	138 (16)	138 (16)
Body-mass index* (kg/m²)	28·6 (5·6)	28·7 (5·3)
Quality of life score, MLHFQ	43·5% (23·1)	43·2% (23·1)
Medical history		
LVEF	22·7% (5·1)	22·6% (5·3)
Hospitalisation for heart failure in past 12 months		
Yes	593 (49%)	591 (49%)
No	456 (38%)	456 (38%)
Information missing	155 (13%)	157 (13%)
Myocardial infarction	744 (62%)	745 (62%)
Hypertension	725 (61%)	698 (59%)
Unstable angina	267 (22%)	290 (24%)
Stroke	124 (10%)	124 (10%)
Transient ischaemic attack	72 (6%)	76 (6%)
Diabetes mellitus	481 (40%)	478 (40%)
Dyslipidaemia	877 (73%)	875 (73%)
Coronary artery bypass graft surgery	386 (32%)	398 (33%)
Percutaneous coronary intervention	382 (32%)	372 (31%)
Implantable cardioverter defibrillator	315 (26%)	308 (26%)
Cardiac resynchronisation therapy	123 (10%)	130 (11%)
Medical treatment of interest		
ACE-I or ARB	1130 (94%)	1134 (94%)
β blocker	1041 (87%)	1051 (87%)
Diuretic	1130 (94%)	1126 (94%)
Aldosterone antagonist	583 (48%)	608 (51%)
Digoxin	537 (45%)	526 (44%)
Lipid-lowering drug	824 (68%)	828 (69%)
Antiplatelet	833 (69%)	834 (69%)
Antithrombotic drug (warfarin)	390 (32%)	427 (36%)

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Data are number (%) of patients or mean (SD), unless otherwise noted. IMT=immunomodulation therapy. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction. MLHFQ=Minnesota living with heart failure questionnaire. ACE-I=angiotensin-converting enzyme inhibitor. ARB=angiotensin-II receptor blocker. *Safety population.

Table 1: **Baseline characteristics of patients**

Procedures

Device-based immunomodulation therapy (IMT) is a point-of-care outpatient procedure in which a sample of whole autologous blood is exposed ex vivo to controlled amounts of oxidative stress. The VC7000A autologous blood treatment system (Celacade System, Vasogen, Mississauga, ON, Canada) consists of a treatment unit (model VC7001A) and a sterile, single-use, disposable cartridge (model VC7002). For each patient, venous blood (10 mL) was placed in 2 mL of sodium citrate (anticoagulant). The citrated blood sample was immediately transferred to the VC7002 cartridge, which was then inserted into the VC7001A device. The blood sample was exposed to oxygen/ozone gas mixture (ozone concentration of 15·35 g/m³) delivered at a flow rate of 240 mL per min, and ultraviolet light at a wavelength of 253·7 nm) at a temperature of 42·5°C for about 20 min. The treated blood sample was then removed from the system and immediately administered by intragluteal injection to the same individual from whom the blood sample was obtained after an injection of local anaesthetic.

Patients allocated to the placebo group attended treatment sessions according to the same procedure as those allocated to the experimental therapy. The same procedure was used to extract the patient's blood, but rather than being treated by the VC7000A device, the blood was discarded and a masked sample of 10 mL sterile saline was injected intramuscularly within the same time frame. All treatment procedures were completed and related documentation was maintained by study personnel not otherwise involved in the assessment of patients. After randomisation, two treatments were given on consecutive days, followed by a third on day 14. Subsequent treatments were given at 4-week (28 day) intervals for at least 22 weeks or until study completion.

Statistical analysis

ACCLAIM study was an outcome event driven trial. Patients were treated until a minimum of 701 primary endpoint events had taken place. All patients were treated for a minimum of 22 weeks. Interim analyses were done by the data and safety monitoring board after 50% and 75% of the required number of primary events had been recorded. The effect of treatment on the primary endpoint was assessed by Cox proportional hazards modelling. Time-to-event distributions were summarised with Kaplan-Meier curves. Effect of treatment on selected secondary endpoints was reported, in addition to measures of effect sizes, SEs, and CIs. Multiplicity adjustment was not done for secondary endpoint analyses.

Effect of IMT on the primary endpoint was assessed in prespecified subgroups of patients defined on the basis of 20 prerandomisation variables, including age, sex, cause of heart failure, history of myocardial infarction, NYHA functional class, LVEF, medication usage, and presence of resynchronisation therapy or implantable defibrillator. Effect sizes and CIs were measured for all subgroup strata. Uniformity of treatment effect was assessed by a Cox proportional hazards analysis, which provided an assessment of the homogeneity of the effect of therapy. Two associations were investigated: (1) direct or main effect of the subgroup on primary endpoint; and (2) degree to which the subgroup strata affected the association between therapy and the primary endpoint (effect modifier or interaction).

The Minnesota living with heart failure questionnaire (MLHFQ)[19] was administered before randomisation (baseline) and every 3 months until end of study. Change in scores between baseline and each follow-up assessment was calculated for all scale scores and treatment group. An analysis of covariance model was used to examine the overall effect of treatment on quality of life.

The intent-to-treat population was defined as all patients randomised, and the safety population included all randomised patients who received at least one study treatment. This study is registered with ClinicalTrials.gov, number NCT00111969.

Role of the funding source

Members of the medical and scientific departments of the sponsor Vasogen supported the work of the steering committee, data and safety monitoring board, and central endpoint committee, but did not make any scientific or research decisions independent of these committees.

Results

2426 patients were randomised at 177 centres in seven countries (Canada, Denmark, Germany, Israel, Norway, Poland, and the USA) between June, 2003 and May, 2005 (figure 1). Table 1 shows the baseline characteristics. Patients were predominately white men with severe LV systolic dysfunction. Almost all patients were in NYHA class II or III. Medical history of patients included myocardial infarction and diabetes mellitus, and about two-thirds of patients had previously undergone coronary artery bypass surgery or percutaneous revascularisation procedure. Medically, patients were very well treated as shown by most receiving either an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker and a β blocker at baseline. Antiplatelet agents and warfarin were also used. Implanted defibrillators were present at baseline in about a quarter of patients and about a tenth had a resynchronisation pacemaker in place.

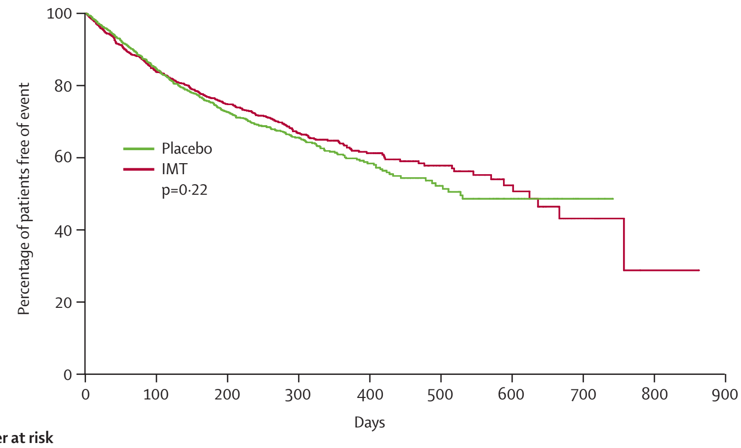

Figure 2: **Kaplan-Meier estimates of time to primary endpoint**
IMT=immunomodulation therapy.

	IMT (n=1204)	Placebo (n=1204)	Hazard ratio (95% CI)	p value*
Primary outcome				
Death from any cause or cardiovascular hospitalisation	399 (33%)	429 (36%)	0·92 (0·80–1·05)	0·22
Secondary outcome				
Death or hospitalisation from any cause	534 (44%)	557 (46%)	0·96 (0·85–1·08)	0·51
Death from any cause or hospitalisation for heart failure	265 (22%)	292 (24%)	0·88 (0·75–1·04)	0·15
Death from any cause	128 (11%)	117 (10%)	1·08 (0·84–1·39)	0·53
Cardiovascular hospitalisation	356 (30%)	375 (31%)	0·94 (0·81–1·09)	0·39
All-cause hospitalisation	505 (42%)	519 (43%)	0·98 (0·86–1·10)	0·70
Hospitalisation for heart failure	210 (17%)	221 (18%)	0·93 (0·77–1·04)	0·44
Cardiovascular death†	75 (6%)	58 (5%)	1·28 (0·91–1·80)	0·16
Cardiovascular death or sudden death†	106 (8·8%)	96 (8·0%)	1·09 (0·83–1·44)	0·53
Cardiovascular events composite	100 (8·3%)	106 (8·8%)	0·95 (0·72–1·24)	0·70
MLHFQ quality of life score	−6·9	−5·2	··	0·04

Data are number (%), unless otherwise indicated. IMT=immunomodulation therapy. MLHFQ=Minnesota living with heart failure questionnaire *Log-rank test for all comparisons apart from MLHFQ quality of life score, which was compared with ANCOVA. †Central endpoint committee (CEC) originally classified cardiovascular death and sudden death separately. However, the two categories were aggregated post-hoc. The criteria used by the CEC to designate cardiovascular death compared with those used to designate sudden death supported the aggregation since the occurrences of sudden death, in which promontory symptoms had not been identified, were probably cardiac in origin.

Table 2: **Summary of study events**

By the end of the study, we recorded a primary endpoint in a total of 828 patients in the two groups (figure 2 and table 2). Death was the primary event in 97 patients (43 *vs* 54 in the IMT and placebo groups, respectively) and hospitalisation for cardiovascular disease was the secondary event in a total of 731 patients. A significant difference was noted in least-square mean change for quality of life score as measured by the MLHFQ in favour of IMT at study end compared with baseline (table 2).

A total of 245 deaths were reported throughout the course of the trial. The 1-year mortality was 117 (10%) in the IMT group and 102 (9%) in the placebo group. 338 (28%) patients in the IMT group and 358 (30%) in the placebo group were admitted (608 and 618 hospital admissions, respectively) at least once for a cardiovascular cause at 1 year. 195 (16%) patients receiving IMT were admitted (334 hospitalisations) at least once for heart failure at 1 year compared with 207 (17%) receiving placebo (361 hospitalisations). Other than for the quality of life score, there was no difference in secondary endpoints between the two groups (table 2). However, there was a slight, but non-significant, difference in favour of IMT in the mean change from baseline in serum C-reactive protein at week 14 (–0·28 mg/L *vs* 0·38 mg/L for the IMT and placebo groups, respectively; p=0·052). This difference could be seen until week 26 (–0·20 mg/L *vs* 0·33 mg/L for the IMT and placebo groups, respectively; p=0·15).

Adverse events and serious adverse events reported in the trial were equally distributed between the IMT and placebo groups (table 3). Proportion of patients who permanently discontinued study treatment as a result of adverse events (including deaths) was about 11% in both groups. More than 26 500 injections were administered during the trial. Of note, at baseline, 2147 (88%) patients received either an antiplatelet agent (aspirin or clopidogrel [1664, 69%] or warfarin [817, 34%], or both [332, 14%]). Frequency of injection-site bruising or haemorrhage in patients receiving antithrombotic agent warfarin was 2·6% (ten events in 390 patients) and 1·9% (eight events in 427 patients) in the IMT and placebo groups, respectively. No serious injection-site adverse events were reported. Compared with placebo, adverse events related to injection site were more frequent in the IMT group; however, in both groups, the frequency of injection-site adverse events as a percentage of total adverse events was less than 5%; all injection-site-related adverse events associated with IMT were mild (89%) or moderate (11%). Frequency of adverse events at injection site as a percentage of total injections in each group was less than 2% (table 3). No clinically relevant differences between the groups were noted for standard laboratory safety measurements, vital signs, or electrocardiographic indices.

Effect of IMT on death from any cause or first cardiovascular hospitalisation for subgroups was defined on the basis of 20 prerandomisation variables (figure 3). Interaction between treatment and NYHA class and between treatment and history of myocardial infarction was significant. In the 689 NYHA class II patients, 92 primary endpoint events were recorded in the IMT group compared with 124 in the placebo (hazard ratio 0·61; 95% CI 0·46–0·80; p=0·0003). In patients (n=919) with no history of myocardial infarction, 105 primary endpoint events occurred in the IMT group, versus 138 in the placebo group (0·74; 0·57 to 0·95; p=0·02). Figure 4 shows the effect of active treatment in these two subgroups.

	IMT (n=1205)	Placebo (n=1207)
Serious adverse events*		
Total number	1358	1355
Total number of patients with ≥1	544 (45%)	567 (47%)
Cardiac	337 (28%)	375 (31%)
Surgical and medical procedures	125 (10%)	115 (10%)
Infections	89 (7%)	89 (7%)
Vascular	59 (5%)	55 (5%)
Renal and urinary	44 (4%)	35 (3%)
Injury and procedural complications	33 (3%)	26 (2%)
Gastrointestinal	31 (3%)	50 (4%)
Respiratory	28 (2%)	24 (2%)
Malignant disease	26 (2%)	19 (2%)
Adverse events		
Total number	6761	6921
Total number of patients with ≥1	1001 (83%)	1014 (84%)
Cardiac	574 (48%)	620 (51%)
Infections	422 (35%)	452 (37%)
General and injection site	292 (24%)	256 (21%)
Gastrointestinal	270 (22%)	324 (27%)
Musculoskeletal	274 (23%)	268 (22%)
Investigations	246 (20%)	231 (19%)
Nervous system	243 (20%)	251 (21%)
Vascular	200 (17%)	200 (17%)
Metabolism and nutrition	195 (16%)	193 (16%)
Injection site adverse events		
Total number of injections	13 358	13 341
Total number of patients with ≥1	137 (11%)	56 (5%)
Total number	216	81
As a proportion of total adverse events	3·2%	1·2%
As a proportion of total injections	1·6%	0·6%
Proportion classified as mild	192 (89%)	66 (81%)
Injection site adverse event breakdown, number of events		
Pain	142 (66%)	35 (43%)
Discomfort	30 (14%)	26 (32%)
Haemorrhage	15 (7%)	5 (6%)
Bruising	12 (6%)	6 (7%)
Burning	5 (2%)	1 (1%)
Other	12 (6%)	8 (10%)

Data are number (% of total patients within treatment group), unless otherwise noted. *Patients counted once within each body system.

Table 3: Most frequently occurring adverse events

Discussion

We have shown no difference in the composite endpoint of death from any cause or first admission for cardiovascular reasons between patients on IMT and those on placebo. The ACCLAIM study achieved its enrolment goals and the number of target events, but it did not meet its primary endpoints or most of its secondary outcome endpoints. Quality of life (a secondary endpoint) was improved in the IMT group compared with the placebo group. IMT was safe as shown by an equal distribution of serious adverse events between the IMT and placebo groups. Importantly, no detrimental haemodynamic effects and no significant imbalances in the frequency of infections or malignancies were recorded.

Absence of benefit on the primary endpoint in the ACCLAIM study was disappointing in view of increasing evidence that inflammation plays a part in the progression of heart failure. Indeed, the association between TNFα concentrations and chronic heart failure severity encouraged previous investigators to undertake studies aimed at assessing the effects of neutralising TNFα activity in patients with chronic heart failure. However, this highly specific anticytokine approach has produced disappointing results.[5,6] Various explanations for the failure of these trials have been proposed, which include the possibility that the biological agents used to antagonise TNFα activity were intrinsically toxic or might have stimulated rather than neutralised TNFα activity.[4] Also, TNFα is not the only inflammatory mediator that is increased in chronic heart failure.[20,21] Other inflammatory cytokines (eg, interleukin 1, interleukin 6) might have been sufficiently increased to overcome any benefits derived from neutralising TNFα. Further, targeted antiTNFα treatment is not associated with an upregulation of anti-inflammatory mediators that have the potential to restore the balance between inflammatory and anti-inflammatory cytokines.

The immunomodulatory approach used in the ACCLAIM study has proved experimentally to be non-specific, such that no cytokine is blocked or inhibited. Thus, although tissue concentrations of proinflammatory cytokines have been decreased in animal models of inflammation,[22] concentrations of anti-inflammatory cytokines, such as transforming growth factor-β and interleukin 10, were increased, suggesting a rebalance of immune responses. We did not measure cytokine concentrations in the ACCLAIM study and therefore the clinical findings cannot be related to inflammatory markers. This decision was taken because cytokines are locally produced and rapidly degraded and therefore circulating concentrations might not accurately mirror tissue inflammation. Myocardial specimens for tissue analysis were not obtained. However, in an earlier trial assessing patients with peripheral arterial disease, a between-group difference was noted in serum concentrations of the inflammatory marker C-reactive protein in favour of IMT after 12 months.[23] In our study, there was a trend towards a reduction in serum C-reactive protein concentrations in the IMT-treated patients compared with placebo-treated patients. Because other studies have shown that C-reactive protein concentrations are associated with the release of inflammatory cytokines,[24] we believe that these results provide support for an immunomodulatory mechanism of IMT. However, the overall results of the ACCLAIM study suggest that this treatment approach does not have sufficient biological activity to favourably alter either mortality or morbidity in all patients with advanced chronic heart failure.

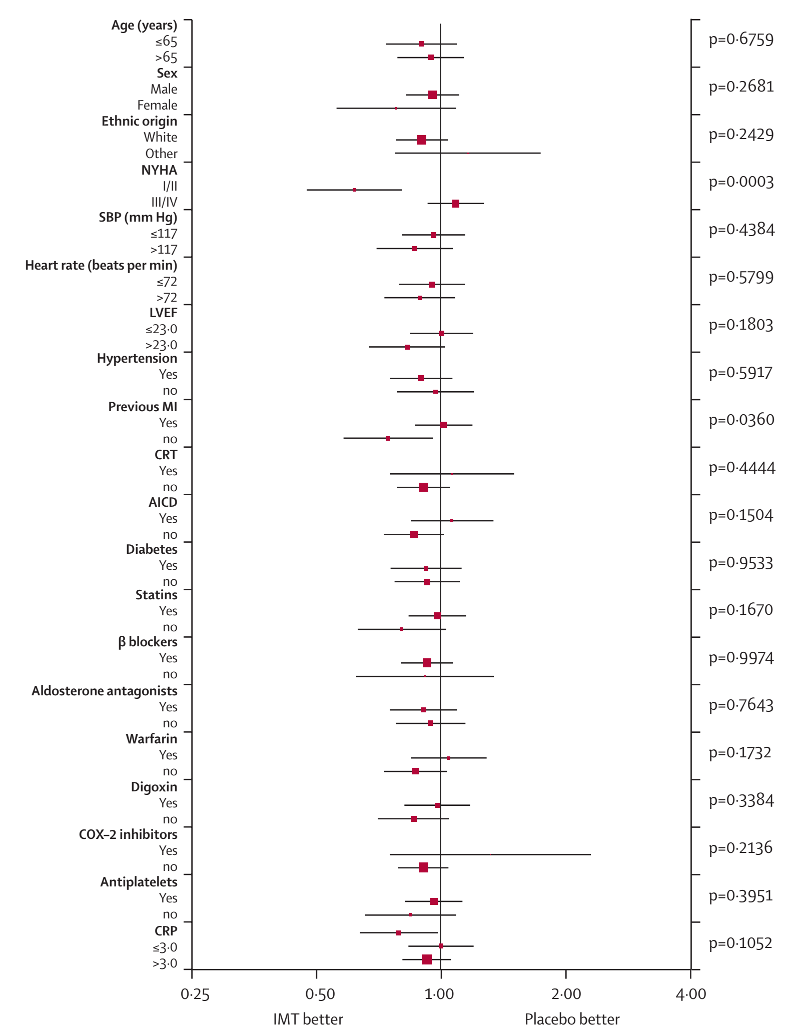

Figure 3: **Effect of immunomodulation therapy (IMT) on death from any cause or cardiovascular hospitalisation in prespecified subgroups**
NYHA=New York Heart Association. SBP=systolic blood pressure. LVEF=left ventricular ejection fraction. MI=myocardial infarction. CRT=cardiac resynchronisation treatment. AICD=automatic implanted cardiac defibrillator. COX=cyclo-oxygenase. CRP=C-reactive protein. Point estimates of hazard ratios are shown with 95% CIs (horizontal lines). Size of point estimate is proportional to the number of patients in each subgroup. p values are for heterogeneity.

Prospective analysis of prespecified subgroups identified two distinct populations that benefited from IMT—patients with NYHA class II symptoms and those without a history of myocardial infarction. About 700 patients had NYHA class II symptoms (those with and those without a history of myocardial infarction); IMT reduced the risk of primary endpoint in this cohort by 39%. Another subgroup that benefited was a cohort of more than 900 patients without a history of myocardial infarction in whom IMT was associated with a 26% risk reduction. Both of the subgroups—compared with the

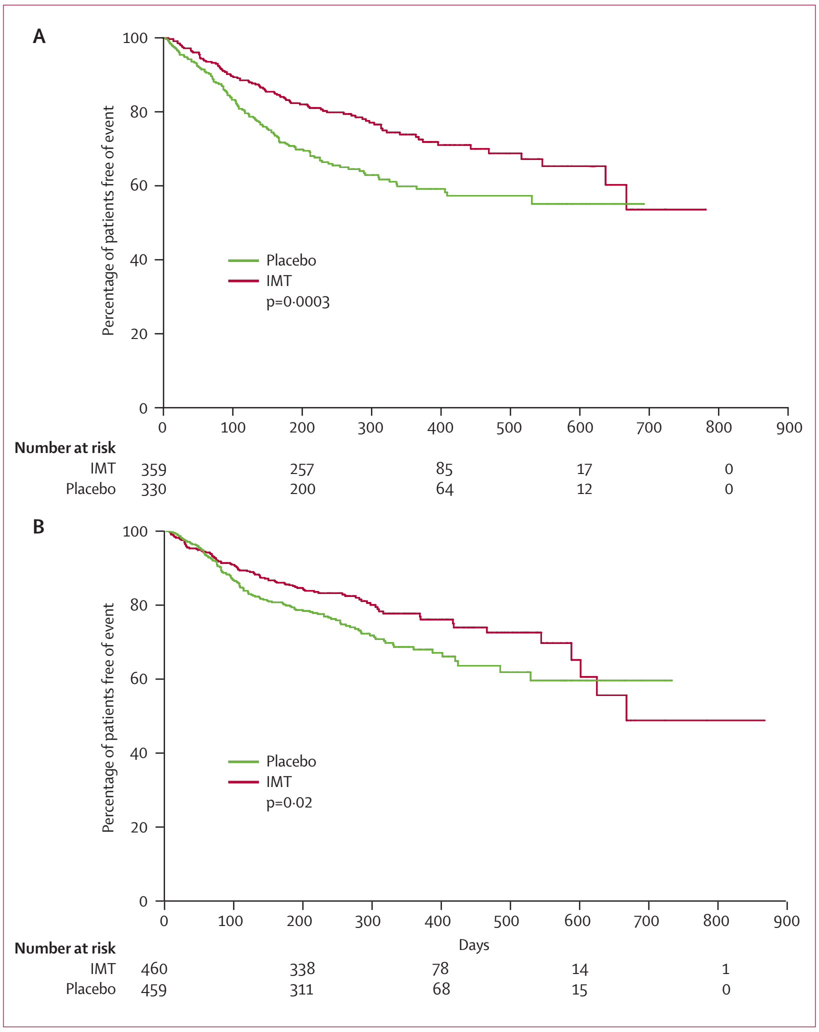

***Figure 4:* Kaplan-Meier estimates of time to primary endpoint in the New York Heart Association class II subgroup (upper) and in the subgroup without a history of myocardial infarction (lower)**
IMT=immunomodulation therapy. The primary endpoint was the composite of death from any cause or first cardiovascular hospitalisation.

entire population—consisted of younger patients with baseline variables that were characteristic of less severe disease—ie, increased ejection fraction, haemoglobin concentrations, systolic blood pressure, and body-mass index; and, reduced C-reactive protein concentrations.

The explanation for these results might lie in the mechanisms by which immune cardiac injury arises—eg, experimental cardiac-restricted overexpression of TNFα-induced hypertrophy and subsequent progressive cardiac dilation and death.[25] Blockage of TNFα prevented development of hypertrophy and injury;[26] however, once TNFα-induced injury is established, antiTNFα therapy offers no therapeutic benefit. The negative findings of the results of the randomised etanercept worldwide evaluation (RENEWAL) trial are consistent with this proposition.[6] For antiTNFα therapy to be clinically effective, an intervention would need to be started early, before development of permanent cellular damage. Consistent with this opinion are the findings of a clinical trial in which antiTNFα therapy started within the first 2 weeks of cardiac transplantation reduced the development of cardiac allograft hypertrophy, which develops in association with high concentrations of intramyocardial TNFα.[27] Taken together these results suggest that TNFα-induced cardiac injury is preventable, but only if started before permanent myocyte injury occurs. This hypothesis is consistent with the results of the ACCLAIM study, in which a clinical benefit was seen in subgroups with less advanced disease—ie, patients without a history of myocardial infarction and those with a history of myocardial infarction who had not yet progressed to an increased symptomatic or refractory stage of myocardial damage.

A similar frequency of adverse events, including serious adverse events, was reported by patients given IMT compared with those in the placebo group. Specifically, no demonstrable effect on vital signs or renal function was recorded as shown by the adverse events and laboratory profiles. These findings are of relevance because an increasing number of patients are now given haemodynamically and metabolically active drugs. Another similarity was noted in the rates of both infection and cancer between the IMT and placebo groups, attesting to the safety of active treatment. Although an imbalance in the occurrence of malignant diseases was recorded in a previous IMT trial assessing patients with peripheral arterial disease,[23] the overall occurrence of confirmed or suspected malignant diseases in ACCLAIM—a trial with four times as many patients and longer treatment exposure time—was similar (p=0·30, Fisher's exact test). In the ACCLAIM study, no particular type of cancer predominated, although an imbalance was seen in reports of colorectal cancer (nine patients in the IMT group and three in the placebo group).

In practice, use of intramuscular injections in patients with heart failure has been constrained because of concern for the development of local haematoma or bleeding, especially among patients on anticoagulant or antiplatelet therapies, or both. In the ACCLAIM study, more than 26 500 intramuscular injections were administered. Antiplatelet or anticoagulant agents were given to about 90% of patients. However, the rate of haemorrhage or bruising was 0·14% of total number of injections administered to patients. Additionally, less than 1% of injections were associated with pain or discomfort at the administration site. The findings of our large study show that intramuscular therapy is both safe and well tolerated in patients with heart failure. Our findings suggest a role for non-specific immunomodulation as a potential treatment for a large segment of the heart failure population—including patients without a history of myocardial infarction (irrespective of their functional NYHA class) and those within NYHA class II. However, this hypothesis needs to be tested in an adequately powered confirmatory trial.

Contributors
All authors, as members of the study steering committee, were involved in the protocol design and were involved in monitoring the conduct of the trial. All authors participated in data interpretation. GTA and JBY were responsible for the first draft of the report, and all authors contributed to review and revisions. All authors approved the final version of the report.

Conflict of interest statement
All authors served on the steering committee for the ACCLAIM study and each received an honorarium or travel support, or both, from the sponsor for this service. None of the authors received shares or share options in the company. GAT had full access to all the data from the study and had final responsibility for the decision to submit the manuscript for publication.

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Steering Committee: James Young (Chair), The Cleveland Clinic, Cleveland, OH, USA; Stefan Anker, Charité, Campus Virchow-Klinikum, Berlin, Germany; Robert C Bourge, University of Alabama at Birmingham, Birmingham, AL, USA; Wilson Colucci, Boston University School of Medicine, Boston, MA, USA; Barry Greenberg, University of California San Diego Medical Center, San Diego, CA, USA; Per Hildebrandt, Frederiksberg Hospital, Frederiksberg, Denmark; Andre Keren, Hadassah University Hospital, Jerusalem, Israel; Michael Motro, Chaim Sheba Medical Center, Tel-Hashomer, Israel; Jan Erik Otterstad, Hospital of Vestfold, Toensberg, Norway; Craig Pratt, Methodist Hospital, Houston, TX, USA; Piotr Ponikowski, Military Hospital, Wroclaw, Poland; Jean Lucien Rouleau, Faculty of Medicine, Universite de Montreal, Montreal, QC, Canada; Francois Sestier, Hotel Dieu du CHUM, Center de Recherche, Montreal, QC, Canada; Guillermo Torre-Amione, Methodist Hospital, Houston, TX, USA; and Bernhard Winkelmann, Kardiologische Gemeinschaftspraxis, Frankfurt, Germany.

Central Endpoint Committee: Robert C Bourge (Chair), University of Alabama at Birmingham, Birmingham, AL, USA; Victoria Bernstein, Vancouver Hospital and Health Sciences Center, Vancouver, BC, Canada; Garrie J Haas, Davis Heart and Lung Research Institute, Columbus, OH, USA; and T Barry Levine, Allegheny General Hospital, Pittsburg, PA, USA.

Data and Safety Monitoring Board: John Cairns (Chair), University of British Columbia, Vancouver, BC, Canada; Barry Massie, San Francisco VA Medical Center, San Francisco, CA, USA; and William Wilkinson, Duke University Medical Centre and Health System, Durham, NC, USA.

Statistician: Lemuel A Moyé, University of Texas Health Science Center, Houston, TX, USA.

Principal Investigators (listed by top recruiting sites within country): *Canada*—H Haddad, Ottawa, ON; C Maranda, Westmount, QC; G Proulx, Sainte-Foy, QC; J O Parker, Kingston, ON; N S Giannetti, Montreal, QC; T Rebane, Mississauga, ON; P Klinke, Victoria, BC; M Arnold, London, ON; F Sestier, Montreal, QC; N Racine, Montreal, QC; S Vizel, Cambridge, ON; D L Isaac, Calgary, AB; C Constance, Montreal, QC; R Leader, Ajax, ON; J D Parker, Toronto, ON; R K Bhargava, Oshawa, ON; T Huynh, Montreal, QC; S Lepage, Sherbrooke, QC; J M Cherry, Scarborough, ON; R Chun, Newmarket, ON; D Marr, Saint John, NB; D Delgado, Toronto, ON; D Saulnier, Levis, QC; G Moe, Toronto, ON; C Michel, Montreal, QC; Y Pesant, Saint-Jerome, QC; V Bernstein, Vancouver, BC; D E Manyari, Surrey, BC; P Boucher/J Lenis, Longueuil, QC; R Dupuis, Thetford-Mines, QC; G Gosselin, Terrebonne-Sector Lachanaie, QC; F Sandrin, Pointe-Claire, QC; J Howlett, Halifax, NS; and A R J Rajakumar, Saskatoon, SK. *Denmark*—L Koeber, Copenhagen; K Egstrup, Svendborg; P Eliassen, Holback; P Sogaard, Hellerup; C Torp-Pedersen, Copenhagen; K Skagen, Herlev; P Hilderbrandt, Roskilde; J Schou, Kobenhavn S; T Nielsen, Esbjerg; G Jensen, Hvidovre; L Videbaek, Odense; and J Rokkedal, Glostrup. *Germany*—S P Denny, Georgsmarienhutte; M Natour, Heidelberg; U Desaga, Hamburg; V Von Behren, Wiesbaden; R Piechatzek, Goelitz; B Pieske, Gottingen; M Dursch, Frankfurt; S Anker, Berlin-Wedding; T Muenzel, Mainz; J Hein, Marburg; G E Von Manteuffel, Marburg; K Weyland, Ingelhleim; T Dreykluft, Berlin-Steglitz; G Scholz, Offenbach; M Buerke, Halley-Saale; A Schmidt, Offenbach; W Sehnert, Dortmund; H P Schultheiss, Berlin; F X Kleber, Berlin-Marzahn; H Naegele, Reinbek; R Lehmann, Berlin; T Drescher, Stuhr-Brinkum; D Wietholt, Uelzen; M F H Schoenauer, Lelipzig; J Bonarius, Greifenstein-Beilsten; and V Mitrovic, Bad Nauheim. *Israel*—M Eldar/D Friemark, Tel-Hashomer; A Marmor, Hadera; L Reisin, Tel-Aviv; A Shotan, Zrifin; C Lotan, Afula; D Sheps, Haifa; J M Dreyfus, Be'er Sheva; A Battler, Petach Tikva; A Caspi, Jerusalem; B S Lewis, Jerusalem; T Rosenfeld, Ashkelon; J Rozenman, Safed; T A Weiss, Jerusalem; Z Vered, Haifa; D David, Rehovot; D Tzivoni, Jerusalem; R Zimlichman, Holon; and U Rosenschein, Kfar-Saba. *Norway*—T Finjord/I Asmussen, Foerde; J E Otterstad, Toensberg; J Kjekshus, Oslo; T I Stakkevold, Namsos; V Bonarjee, Stauvanger; and E S P Myhre, Kristiansand. *Poland*—P Ponikowski, Wroclaw; W Pluta, Opole; L Polonski, Zabrze; J Hiczkiewicz, Nowa Sol; M Ujda, Stalowa Wola; M Krzeminska-Pakula, Godz; K Kuc, Zielona Gora; R Szelemej, Watbrzych; J Tarchalski, Kalisz; T Pasierski, Warsaw; P Podolec, Krakow; M Ogorek, Piotrkow Trybunalski; G Opolski, Warsaw; M Dluzniewski, Warsaw; M Niemczyk, Wolomin; A Opadczuk, Warsaw; M Mierzejewski, Warsaw. *USA*—C S Liang, Rochester, NY; G Torre-Amione, Houston, TX; J B Young, Cleveland, OH; L C Egbujiobi, Beloit, WI; S K Krueger, Lincoln, NE; M E McIvor, St Petersburg, FL; B C Peart, Tucson, AZ; F A McGrew, Germantown, TN; A Barbagelata/E R Schwarz, Galveston, TX; K F Adams, Chapel Hill, NC; E J Kosinski, Bridgeport, CT; R L Bellinger, Sacramento, CA; I S Anand, Minneapolis, MN; S Wagner, Louisville, KY; D Mann, Houston, TX; B Czerska, Detroit, MI; M R Costanzo, Naperville, IL; R M Kipperman, Oklahoma, OK; J T Heywood, Loma Linda, CA; R C Bourge/L J Pinderski, Birmingham, AL; R J Weiss, Aubrun, ME; D J Kereiakes, Cincinnati, OH; M A Frais, Hot Springs, AR; M Colvin-Adams, Minneapolis, MN; J Kennett, Columbia, MO; R G Zoble, Tampa, FL; R R Zimmer, Philadelphia, PA; S W Halpern, Santa Rosa, CA; D Banks/J K Ghali, Shrevport, LA; G E Peterson, Des Moines, IA; I K Niazi, Elkhorn, WI; L N Ferrier, Rapid City, SD; S H Dunlap, Chicago, IL; R C Bogaev, San Antonio, TX; D J Lenihan, Houston, TX; A S Anderson, Chicago, IL; D M McNamara/S Murali, Pittsburgh, PA; N L Pereira, Charleston, SC; D Bernard, San Diego, CA; R Delgado, Houston, TX; B S Clemson, Peoria, IL; K Vijaraghavan, Scottsdale, AZ; R Gilmore, Lake Charles, LA; J R See, Santa Ana, CA; T B Levine, Pittsburg, PA; M L Kukin, New York City, NY; R Carhart, Syracuse, NY; R J Alvarez, West Reading, PA; L E Wagoner, Cincinnati, OH; D D Schoken, Tampa, FL; W L Meengs, Petoskey, MI; E Sonnenblick/T LeJemtel, Bronx, NY; M J Imburgia, Louisville, KY; A Patel, Boston, MA; S K Gulati, Charlotte, NC; D Finkielstein/J Kalman, New York City, NY; E M Gilbert, Salt Lake City, UH; K W Roush, Toledo, OH; E M Roth, Cincinnati, OH; A Heroux, Maywood, IL; W Levy, Seattle, WA; G Gibbs, La Grange, IL; H Meilman, Baltimore, MD.

References

1 Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. *J Am Coll Cardiol* 2005; **46:** 1116–43.

2 Swedberg K, Cleland J, Dargie H, et al. Guideline for the diagnosis and treatment of chronic heart failure: The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; **26:** 1115–40.

3 Ramasubbu K, Oliveira G, Torre-Amione G. Novel therapies for heart failure: focus on anti-inflammatory strategies. *Congest Heart Fail* 2006; **12:** 153–59.

4 Mann DL. Inflammatory mediators and the failing heart: past, present and the foreseeable future. *Circ Res* 2002; **91:** 988–98.

5 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.

6 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.

7 Parrillo JE, Cunnion RE, Epstein SE, et al. A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. *N Engl J Med* 1989; **321:** 1061–68.

8 Gullestad L, Aass H, Fjeld JG, et al. Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. *Circulation* 2001; **103:** 220–25.

9 Staudt A, Schaper F, Stangl V, et al. Immunohistological changes in dilated cardiomyopathy induced by immunoadsorption therapy and subsequent immunoglobulin substitution. *Circulation* 2001; **103:** 2681–86.

10 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:** 890–98.

11 Voll RE, Herrmann M, Roth EA, Stach C, Kalden JR, Girkontaite I. Immunosuppressive effects of apoptotic cells. *Nature* 1997; **390:** 350–51.

12 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.

13 Babaei S, Stewart DJ, Picard P, Monge JC. Effects of VasoCare therapy on the initiation and progression of atherosclerosis. *Atherosclerosis* 2002; **162:** 45–53.

14 Shivji GM, Suzuki H, Mandel AS, Bolton AE, Sauder DN. The effect of VAS972 on allergic contact hypersensitivity. *J Cutan Med Surg* 2000; **4:** 132–37.

15 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:** 40–46.

16 Torre-Amione G, Sestier F, Radovancevic B, Young J. Effects of a novel immune modulation therapy in patients with advanced chronic heart failure. *J Am Coll Cardiol* 2004; **44:** 1181–86.

17 Torre-Amione G, Bourge RC, Colucci WS, et al. A study to assess the effects of a broad-spectrum immune modulation therapy on mortality and morbidity in patients with chronic heart failure: the ACCLAIM trial rationale and design. *Can J Cardiol* 2007; **23:** 369–76.

18 Moyé LA. Statistical reasoning in medicine: the intuitive p value primer. 2nd edn. New York: Springer-Verlag, 2006.

19 Rector T, Kubo S, 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; **3:** 198–209.

20 Matsumori A, Yamada T, Suzuki H, Matoba Y, Sasayama S. Increased circulating cytokines in patients with myocarditis and cardiomyopathy. *Br Heart J* 1994; **72:** 561–66.

21 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:** 1201–06.

22 Bolton AE. Biologic effects and basic science of a novel immune modulation therapy. *Am J Cardiol* 2005; **95:** 24C–29C.

23 Olin JW, ed. 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; March 11–14, 2006, Atlanta, GA. Late-Breaking Clinical Trials I.

24 Castoldi G, Galimberti S, Riva C, et al. Association between serum values of C-reactive protein and cytokine production in whole blood of patients with type 2 diabetes. *Clin Sci* 2007; **113:** 103–08.

25 Kubota T, McTierman 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.

26 Bozkurt B, Kribbs SB, Clubb FJ, et al. Pathophysiologically relevant concentrations of tumor necrosis factor-alpha promote progressive left ventricular dysfunction and remodeling in rats. *Circulation* 1998; **97:** 1382–91.

27 Torre-Amione G, Wallace CK, Young JB, et al. The effect of etanercept on cardiac transplant recipients: a study of TNF α antagonism and cardiac allograft hypertrophy. *Transplantation* 2007; **84:** 480–83