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

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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,12 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.1 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.1 Despite evidence for the role of inflammation in the progression of heart failure, no specific therapy addressing this pathophysiological mechanism exists, and interventions targeting a specific inflammatory cytokine—such as tumour necrosis factor (TNF)α—have been disappointing.14 However, a non-specific approach to modulation of the immune response might lead to clinical benefit in patients with chronic heart failure.15 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,16 intravenous immunoglobulin,1 and immunoadsorption therapy.17 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.18,19 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.20 Results from preclinical studies using apoptotic cells as the immunomodulatory stimulus have shown reductions in inflammation and in production of inflammatory mediators,21–23 increases in anti-inflammatory cytokine expression, and decreased cell death.24 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...
administration resulted in a reduction of both all-cause mortality and hospital admissions. 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. 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 α=0.049 (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. 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](image-url)

**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

**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).
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) 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.

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.

### 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. 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. Also, TNFα is not the only inflammatory mediator that is increased in chronic heart failure. 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, 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. 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, 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.

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
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. Blockage of TNFα prevented development of hypertrophy and injury; 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. 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. 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, 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.
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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