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Effects of a Novel Immune Modulation Therapy in Patients With Advanced Chronic Heart Failure

Results of a Randomized, Controlled, Phase II Trial

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OBJECTIVE We sought to determine whether a novel, non-pharmacological form of immune modulation therapy (IMT), shown experimentally to reduce inflammatory and increase anti-inflammatory cytokines, improved outcomes in patients with advanced heart failure (HF).

BACKGROUND Immune activation contributes to the progression of HF, but treatments directed against inflammation have been largely unsuccessful.

METHODS Seventy-five HF patients (New York Heart Association [NYHA] functional class III to IV) were randomized to receive either IMT (n = 38) or placebo (n = 37) in a double-blind trial for six months, with continuation of standard HF therapy. Patients were evaluated using the 6-min walk test, changes in NYHA functional class, cardiac function, and quality of life assessments, as well as occurrence of death and hospitalization.

RESULTS There was no between-group difference in 6-min walk test, but 15 IMT patients (compared with 9 placebo) improved NYHA functional classification by at least one class ($p = 0.140$). The Kaplan-Meier survival analysis showed that IMT significantly reduced the risk of death ($p = 0.022$) and hospitalization ($p = 0.008$). Analysis of a clinical composite score demonstrated a significant between-group difference ($p = 0.006$). There was no difference in left ventricular ejection fraction, but there was a trend toward improved quality of life ($p = 0.110$).

CONCLUSIONS These preliminary findings are consistent with the hypothesis that immune activation is important in the pathogenesis of HF and establish the basis for a phase III trial to define the benefit of IMT in chronic HF. (J Am Coll Cardiol 2004;44:1181–6) © 2004 by the American College of Cardiology Foundation

There is convincing evidence that inflammation has a role in heart failure (HF). In experimental models, inflammatory cytokines promote left ventricular remodeling (1) and contractile dysfunction (2,3), and uncouple myocardial beta-adrenergic receptors (4). Moreover, cardiac-specific overexpression of tumor necrosis factor (TNF)-alpha causes cardiomyopathy and premature death (5). Clinically, anti-cytokine therapy (specifically anti–TNF-alpha) has shown disappointing results. These negative outcomes (6,7) are perhaps not unexpected. Because a number of inflammatory cytokines (8) are increased in HF, inhibition of TNF-alpha alone would not overcome functional duplication within the inflammatory cascade. Moreover, anti–TNF-alpha treatment would not be expected to increase anti-inflammatory cytokines.

Support for a less specific approach to immune modulation in HF comes from a series of small trials that documented benefit from steroids (9), intravenous immunoglobulin (10), and immunoadsorption (11).

Recently, preclinical studies have shown that autologous blood exposed ex vivo to oxidative stress and administered intramuscularly decreases the production of inflammatory mediators (12–14), increases anti-inflammatory cytokines, and decreases apoptosis (14). In human trials of peripheral arterial disease, such immune modulation therapy (IMT) was shown to be safe and to improve vascular endothelial function (15) and claudication distance (16). Accordingly, an exploratory study was conducted to compare the safety and efficacy of IMT in patients with chronic HF.

METHODS

Patient selection. This was a four-center study with patients primarily drawn from HF clinics. Individuals ≥18 years of age with New York Heart Association (NYHA) functional class III to IV, chronic HF, left ventricular ejection fraction (LVEF) <40%, and 6-min walk distance <300 m were enrolled. Patients must have been receiving standard medical treatment. Doses of cardiac medications must have been stable for two weeks (beta-blockers for three months) before randomization.

The ethics committees at participating institutions approved the protocol. All patients gave written informed consent.

Study treatment. The method of treatment has been previously described (16). Briefly, venous blood (10 ml) was collected into 2 ml of 4% sodium citrate and transferred to a sterile, single-use container (VC7002, Vasogen Inc., Mississauga, Ontario, Canada) and inserted into the VC7001 Blood Treatment Unit (Vasogen Inc.). There the

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Abbreviations and Acronyms
HF = heart failure
IMT = immune modulation therapy
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
TNF = tumor necrosis factor

blood was exposed to controlled levels of oxidative stress (14.5 ± 1.0 μg/ml O_3 in medical oxygen and ultraviolet light at wavelength 253.7 nm) at a temperature of 42.5 ± 1.0°C for 3 min. Approximately 10 ml of treated blood/citrate mixture was then administered by slow intragluteal injection, together with 1 ml of 2% lidocaine.

Treatment regimen. Patients received active therapy or placebo (10 ml of saline) on two consecutive days, followed by six monthly injections beginning two weeks later. Patients and clinicians were blinded. There was an unblinded operator who drew blood, treated the sample, and administered the treatment injection. This individual was not involved in patient assessments, and unblinded staff had no access to the treatment area.

Study procedures. Table 1 details the conduct of the study. After a screening/wash-out period of 2 to 14 days, there were six months of treatment. Visit 10 (end-of-study) occurred 30 days after the last treatment. Patient assessments including NYHA functional class, 6-min walk distance, Minnesota Living with Heart Failure Quality of Life questionnaire, echo-Doppler, electrocardiogram, and blood and urine samples were obtained at the time points noted. Blinded measures of QTc and QT dispersion (QTd) were performed in patients with evaluable electrocardiograms. The QT intervals were measured from three consecutive beats in leads II and V_4, averaged, and corrected for heart rate using Fridericia's formula; QTd was determined by averaging the QT intervals from three consecutive beats in each lead and calculating the difference between the shortest and longest value.

At the end of study, patients were categorized as improved, unchanged, or worsened according to a clinical composite score modified from Packer (17). Patients were improved if they had not experienced death or hospitalization and had improved NYHA functional class. Patients were worsened if they had a major event or worsening of NYHA functional class.

Statistical analyses. The primary end points were changes in 6-min walk distance and NYHA functional classification. Secondary end points were changes in cardiac function, all-cause mortality, all-cause hospitalizations, and Minnesota Living with Heart Failure Quality of Life questionnaire score. Exploratory analyses included a clinical composite score and change in QTc and QTd.

For end points that had two or more post-treatment measurements, a repeated-measures analysis of variance (ANOVA) was performed. For discrete end points, logistic models were used. Patients withdrawn from therapy for any reason (including death), had the last observation carried forward. Cumulative survival curves for the risk of all-cause mortality and all-cause hospitalization were constructed by the Kaplan-Meier method; differences between the curves were tested for significance using the log-rank statistic. The analyses of other variables were descriptive.

RESULTS

Patients. Seventy-five patients were randomized, 38 to IMT and 37 to placebo (Fig. 1). One patient randomized to IMT received no study treatment and was excluded from all analyses. Another patient randomized to IMT had the final visit postponed; a decision was made before database closure and unblinding not to include this patient's data in efficacy analyses. A total of 5 patients (13.9%) in the IMT and 12 (32.4%) in the placebo group discontinued treatment prematurely. As shown in Table 2, the groups were well matched for all major baseline characteristics. Reasons for study discontinuations are provided in Figure 1.

Table 1. Study Flow Chart

	Screening	Treatment								F/U
Phase of Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Time in Study (Days)	**−14 to −2**	**1**	**2**	**14**	**44**	**74**	**104**	**134**	**164**	**194**
History and examination	X									
Randomization		X								
Treatment		X	X	X	X	X	X	X	X	
Clinical assessment, including adverse events and NYHA functional class	X	X	X	X	X	X	X	X	X	X
6MWD test and MLHF QoL questionnaire	X							X		X
12-lead ECG/2D echo Doppler	X									X
Blood* and urine† samples	X						X			X
Cytokines,‡ BNP, CRP levels	X			X						X

*Electrolytes, blood urea nitrogen, creatinine, total protein, albumin, calcium, phosphorus, glucose, AST (SGOT), ALT (SGPT), ALP (alkaline phosphatase), total bilirubin, direct bilirubin, LDH (hepatitis B antigen, and pregnancy test at visit 1 only); †Dipstick, ‡Interleukin-2, interleukin-10, tumor necrosis factor-alpha, and interferon-gamma.
BNP = brain natriuretic peptide; CRP = C-reactive protein; F/U = follow-up; MLHF = Minnesota Living with Heart Failure questionnaire; NYHA = New York Heart Association; QoL = quality of life; 6MWD = 6-min walk distance.

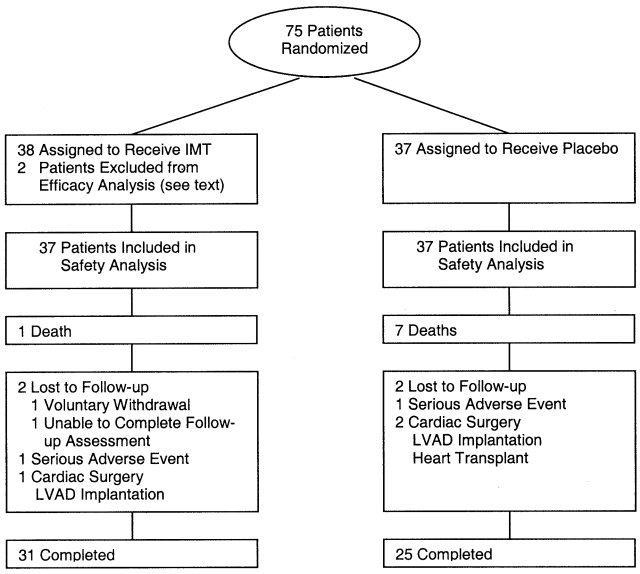

Figure 1. Randomization and flow of patient evaluations. IMT = immune modulation therapy; LVAD = left ventricular assist device.

Primary and secondary efficacy parameters. Mean 6-min walk distance for the IMT group was 218 ± 71 m at baseline and increased 18% at visit 10. For the placebo group, mean 6-min walk distance at baseline was 237 ± 46 m and increased 21% at visit 10 (p = NS). By study end, 15 (41.7%) IMT-treated patients improved their NYHA functional class, whereas 3 (8.3%) worsened, compared with 9 (24.3%) improved and 3 (8.1%) worsened in the placebo group. The percentage of patients with improved status favored the IMT group at visit 10 (p = 0.140).

Kaplan-Meier survival analyses showed that IMT signif-

Table 2. Demographics and Other Baseline Characteristics: Safety Population

	Placebo n = 37	IMT n = 37
Age, yrs	60.3 ± 11.1	63.0 ± 13.4
Male, n (%)	25 (67.6)	26 (70.3)
White, n (%)	25 (67.6)	26 (70.3)
NYHA functional class III/IV, n (%)	36/1 (97.3/2.7)	37/0 (100/0)
LVEF, %	21.5 ± 7.5	22.8 ± 7.8
Previous myocardial infarction	20 (54.1)	16 (43.2)
Previous coronary revascularization	13 (35.1)	13 (35.1)
Diabetes	9 (24.3)	16 (43.2)
Systolic blood pressure	111.2 ± 14.9	116.5 ± 19.5
Diastolic blood pressure	71.7 ± 9.9	71.5 ± 8.7
Heart rate	73.0 ± 12.9	73.7 ± 11.5
BNP (pg/ml)	345.7 ± 387.1	432.5 ± 414.6
Medication use, n (%)		
ACE inhibitor	28 (75.7)	28 (75.7)
Angiotensin-II receptor blocker	5 (13.5)	5 (13.5)
Digitalis	31 (83.8)	30 (81.1)
Beta-blocker	18 (48.6)	20 (54.1)
Diuretics	36 (97.3)	35 (94.6)
Spironolactone	19 (51.4)	15 (40.5)

Data are expressed as mean ± SD or n (%).

ACE = angiotensin-converting enzyme; BNP = brain natriuretic peptide; IMT = immune modulation therapy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

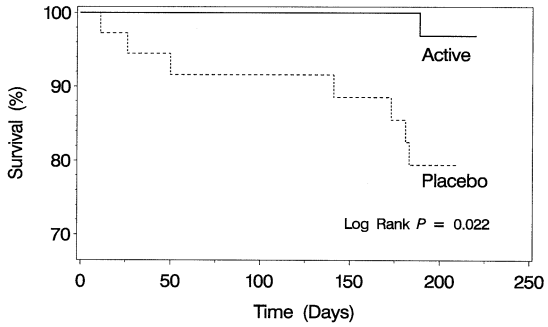

Figure 2. Kaplan-Meier estimates of the probability of survival in the immune modulation therapy and placebo groups. The difference was significant (p = 0.022; log-rank test).

icantly reduced the risk of death (p = 0.022) and of hospitalization (p = 0.008) (Figs. 2 and 3). Patients with at least one hospitalization (33.3% vs. 56.8%; p = 0.061, Fisher exact test) and total number of hospitalizations/patient (0.7 vs. 1.1; p = 0.060, Wilcoxon test) favored IMT. Seven of 12 first hospitalizations in IMT-treated patients were for cardiovascular indication compared with 17 of 21 in the placebo group. There were no between-group differences in LVEF or circulating levels of interferon-gamma, TNF-alpha, interleukin-6, interleukin-10, brain natriuretic peptide, and C-reactive protein (Table 3). Change in the Minnesota Living with Heart Failure Quality of Life questionnaire from baseline trended in favor of IMT (12.2 vs. 4.5 point improvement, last observation carried forward, p = 0.110).

Although deaths in this trial were not adjudicated, review of clinical records revealed that four of seven placebo deaths were probably arrhythmic. Two were rather typical sudden (and unexpected) out-of-hospital deaths. The remaining two patients had worsening HF; one died at home, whereas the other developed ventricular fibrillation in the postoperative period after cardiac surgery.

The remaining three placebo patients all died in-hospital in the postoperative period; one developed pseudomonas septicemia and cardiorenal failure after valve repair and coronary artery bypass grafting; one developed multiorgan failure after heart transplant for worsening HF, and one had

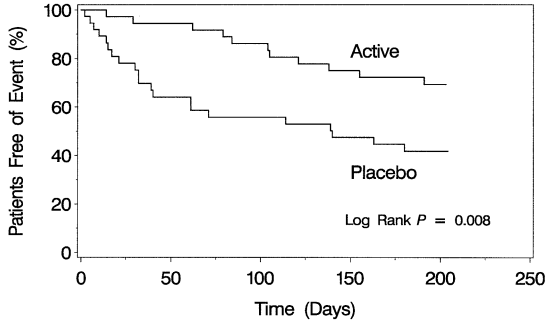

Figure 3. Kaplan-Meier estimates of the probability of hospitalization-free survival in immune modulation therapy versus placebo groups. The difference was significant (p = 0.008; log-rank test).

Table 3. Circulating Cytokine and CRP Values

	n	IMT	n	Placebo	p Value*
TNF-alpha (pg/ml)					
Baseline	38	31.16 ± 12.64	36	33.52 ± 15.96	
Change to F/U	32	−0.50 ± 10.24	24	−2.25 ± 10.32	0.53
IL-6 (pg/ml)					
Baseline	38	9.28 ± 8.19	36	18.45 ± 32.58	
Change to F/U	32	2.45 ± 10.76	24	0.98 ± 15.98	0.68
IFN-gamma (IU/ml)					
Baseline	38	0.17 ± 0.44	36	0.12 ± 0.12	
Change to F/U	32	0.00 ± 0.14	24	0.01 ± 0.09	0.77
IL-10 (pg/ml)					
Baseline	38	3.46 ± 7.59	36	3.69 ± 7.01	
Change to F/U	32	0.48 ± 6.99	23	−1.08 ± 10.24	0.51
CRP (mg/dl)					
Baseline	36	4.48 ± 4.33	36	4.88 ± 3.72	
Change to F/U	31	1.30 ± 4.13	24	0.81 ± 4.29	0.67

*Analysis of variance. Data are expressed as mean ± SD.
CRP = C-reactive protein; F/U = follow-up; IFN = interferon; IL = interleukin; IMT = immune modulation therapy; TNF = tumor necrosis factor.

cardiorenal failure after open reduction and internal fixation of a fractured femoral neck.

The one patient who died in the IMT group succumbed to intestinal bleeding secondary to cholangio carcinoma.

Three of this group died out of hospital; in two, death was sudden and unexpected, whereas the other had experienced progressive HF. The remaining patient experienced cardiac arrest in the postoperative period after cardiac surgery.

Exploratory analyses. Mean QTc decreased in IMT patients (−18 ms; n = 20) compared with an increase in placebo patients (+12 ms; n = 15), resulting in a significant between-group difference at study-end (429 ± 45 ms vs. 463 ± 45 ms, ANOVA, p = 0.035). Similar changes occurred in QTd; end-of-study values were 59.71 ± 22.85 ms vs. 82.08 ± 32.35 ms (p = 0.035).

Clinical composite scores (Fig. 4), showed a significant linear trend in the between-group differences favoring IMT (p = 0.006). Compared with placebo, a greater percentage of IMT patients had improved scores (p = 0.046; Fisher exact test). Similarly, a lower percent of IMT patients had worsened scores (p = 0.010).

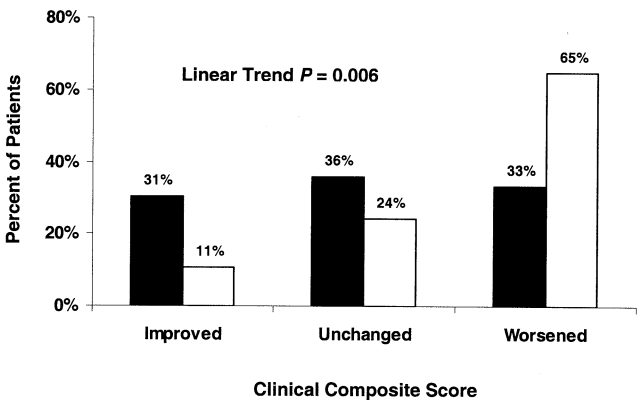

Figure 4. Changes in a clinical composite score from baseline to follow-up visit after six months of treatment with immune modulation therapy **(solid bars)** or placebo **(open bars)**.

Safety. No safety concerns were apparent (Table 4). Almost all patients experienced at least one adverse event. A total of 19 adverse events were judged related to study treatment in the IMT group, compared with 13 in placebo. Only injection-site-related adverse events occurred at a relevantly higher rate in IMT (seven patients) versus placebo (four patients) patients. However, only 12 (4.1%) of the IMT versus 5 (2.0%) of the placebo injections were associated with an injection-site-related adverse event. A total of 14 (37.8%) IMT-treated patients experienced 39 serious adverse events, including 1 death, compared with 67 serious adverse events, including 7 deaths, in 24 placebo patients. No serious adverse events were considered treatment-related.

DISCUSSION

This trial was designed to provide preliminary evidence of safety and efficacy of IMT in chronic HF. Patients had relatively severe HF as depicted by NYHA functional class, LVEF, and exercise capacity. The mortality rate (18.9% at 6.5 months) is higher than observed in some recent HF trials, but is not inconsistent with others (18–20). Although these latter trials had more NYHA functional class IV patients, the LVEFs were similar to the present study; also, a higher percentage of patients enrolled in our trial received spironolactone before randomization, which might have improved functional class.

Neither of the primary efficacy parameters demonstrated significant between-group differences. However, the analysis of these end points was purposefully conservative by imputing missing data as last observation carried forward. Because of the difference in mortality rates, this approach favored the placebo group. Nevertheless, more IMT pa-

Table 4. Frequency of AEs

	Placebo n = 37	IMT n = 37
Patients with ≥1 AE (%)	37 (100)	34 (91.9)
Patients with ≥1 injection site AE (%)	4 (10.8)	7 (18.9)
Total adverse events in study	n = 290	n = 275
Cardiovascular		
Arrhythmia	8 (2.8)	12 (4.4)
Angina pectoris	10 (3.4)	8 (2.9)
Hypotension	4 (1.4)	5 (1.8)
Syncope	3 (1.0)	3 (1.1)
Renal failure	1 (0.3)	2 (0.7)
Injection site		
Edema	0	1 (0.4)
Ecchymosis	1 (0.3)	2 (0.7)
Pain	3 (1.0)	9 (3.3)
Paresthesia	1 (0.3)	0
Infection-related		
General	7 (2.4)	8 (2.9)
Respiratory	25 (8.6)	20 (7.3)

Data are expressed as number (%).
AE = adverse event; IMT = immune modulation therapy.

tients improved their NYHA functional classification than the placebo group ($p = 0.14$).

There was a significant reduction in the risk of death and hospitalization for IMT-treated patients. In addition, the clinical composite score showed a statistical advantage favoring IMT, and there was a trend to improved Minnesota Living with Heart Failure Quality of Life questionnaire.

While the precise mechanism of improved outcomes in IMT-treated patients requires further investigation, the known biological activity of IMT provides a plausible explanation. Current evidence suggests that ex vivo exposure of blood to oxidative stress produces accelerated "senescence" of immune cells such that they undergo apoptosis after intramuscular injection. Interaction of apoptotic cells with immune system macrophages results in decreases in inflammatory and upregulation of anti-inflammatory cytokine production (21). Such modulation of tissue immune responses may favorably influence a number of pathologic processes in HF, including myocardial cell death, left ventricular dysfunction, and electrophysiologic abnormalities.

There were no changes in circulating cytokine levels. However, cytokines are local effectors, and changes in tissue levels are not necessarily reflected in changes in plasma concentrations (22). Moreover, only 55 patients had both baseline and end-of-study measurements. Other than the small sample size, we have no explanation for the lack of impact on brain natriuretic peptide, C-reactive protein, or LVEF. All these issues require assessment in a larger study.

Because four of seven placebo patients most likely suffered arrhythmic deaths, an analysis of QTc and QTd was undertaken to assess arrhythmic substrate in survivors. Baseline QTc was prolonged, and QTc and QTd both increased in the placebo-treated patients but decreased in those receiving IMT, suggesting a reversal of electrophysiologic remodeling (23). More interestingly, because QTc duration may also be a marker of the severity of HF, the reduction in QTc duration observed in the IMT-treated patients may provide another signal of the biological effect of IMT (24). Interpretation of these data should be cautious, however, because analysis was retrospective and conducted in the subset of evaluable patients.

Study limitations. The major limitation of this study is small sample size. This increases the possibility that the high mortality rate in the placebo group and, therefore, the observed benefit from IMT occurred by chance alone. However, it is important to note that, in addition to the reduced mortality in the IMT group, there were also fewer total and cardiovascular hospitalizations, improved composite clinical scores, decreased QTc and QTd in survivors, and a trend toward improved quality of life.

Conclusions. Although a preliminary study that must be interpreted with caution, the findings are consistent with the hypothesis that immune-activation plays an important role in the pathogenesis of HF. Given the lack of detrimental hemodynamic and other adverse effects, IMT could be safely combined with standard HF therapies. The observations from this study have established the basis for a phase III clinical trial to define the full benefit of this novel therapy in chronic HF.

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