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Scientific Update™

Anti-inflammatory Therapy in Heart Failure

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There is increasing evidence supporting the role of immune activation in the pathophysiology of heart failure. As a result, modulation of the immune system represents a novel approach to the treatment of heart failure. To date, studies that have specifically examined tumour necrosis factor-α (TNF-α) – the most studied inflammatory mediator – as the target of intervention have been disappointing. As the inflammatory response involves activation of multiple mediators in addition to TNF-α, a more broad-based approach to immune modulation, including augmentation of anti-inflammatory cytokines, is likely to be more effective. This issue of *Cardiology Scientific Update* reviews the preliminary results of recently presented studies of TNF-α intervention, the potential reasons for the lack of benefit demonstrated in these studies and, as well, the preliminary results of a promising approach to nonspecifically targeted immune activation in heart failure, namely immune modulation therapy.

The role of inflammation and immune activation in the pathogenesis of heart failure

Although it was thought to be predominantly a disorder of left ventricular (LV) pump function, our understanding of the pathophysiology of heart failure has evolved such that it is now thought to be a disorder of neurohormonal activation. Indeed, the neurohormone hypothesis has provided the basis of contemporary pharmacologic treatment of heart failure. More recently, a paradigm shift has occurred to include the role of inflammation and immune activation in the progression of heart failure. There are several lines of evidence supporting the importance of inflammatory cytokines, especially tumour necrosis factor-α (TNF-α) in heart failure. Several studies have demonstrated increased circulating levels of inflammatory cytokines, TNF-α, interleukin 1-ß (IL1-ß), and interleukin-6 (IL-6), as well as increased cardiac expression of TNF-α in patients with heart failure.[1-6] In addition, circulating levels of TNF-α and IL-6 increased in direct relation to the severity of heart failure.[1-3,6] Elevated levels of cytokines and soluble cytokine receptors portend a poor prognosis in patients with heart failure.[1-3,6] The strongest evidence for the cytokine hypothesis is derived from TNF-α transgenic mice. These mice die from heart failure and display a heart failure phenotype that includes reexpression of the fetal gene program, augmented matrix metalloproteinase (MMPs) expression, and activation of apoptotic pathways.[1]

Targeted approach with anti-inflammatory therapy

Since TNF-α is the most well-characterized inflammatory mediator, it is not surprising that investigators have chosen TNF-α as a specific target for therapeutic intervention. Results of 2 studies examining the effect of inhibiting the actions of TNF-α have recently been presented.[7,8]

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Table 1: The RENEWAL Study – Relative risks of death or heart failure hospitalization				
Etanercept SC	25 mg x weekly*	25 mg 2x weekly	25 mg 3x weekly	25 mg 2x and 3x weekly, combined analysis
RECOVER	1.01 (0.72,1.41)	0.17 (0.61,1.04)		
RENAISSANCE		1.12 (0.92,1.58)	1.23 (0.94,1.61)	
RENEWAL, combined analysis		1.08 (0.87,1.33)		1.10 (0.91,1.33)

Data are relative risk (95% CI) compared to placebo, < 1 favours etanercept, > 1 favors placebo
* Not entered into combined analysis for clinical outcome due to limited exposure to drug

SC = subcutaneous

Etanercept in heart failure: The RENEWAL study

Etanercept is a recombinantly produced, chimeric, TNF-α soluble receptor consisting of the p75 receptor linked to the Fc portion of human IgG (TNFR:Fc). The agent has been approved for use in rheumatoid arthritis in the United States. There has only been one preclinical study with etanercept in heart failure. In this study, using a canine model of pacing-induced heart failure, etanercept markedly reduced LV tissue MMPs, accompanied by attenuation of LV remodeling.[9] In a Phase I study of heart failure patients, a single intravenous dose of etanercept suppressed plasma levels of bioactive TNF-α by 85% for 14 days.[10] A subsequent controlled trial in patients with severe heart failure demonstrated that bi-weekly subcutaneous (SC) injections of etanercept for 3 months resulted in a significant dose-dependent improvement in LV ejection fraction, with a trend towards improved composite clinical scores.[11]

The Randomized Etanercept Worldwide Evaluation (RENEWAL) study was a phase III trial comprised of 2 studies of almost identical design:

- The Research into Etanercept: Cytokine Antagonism in Ventricular Dysfunction (RECOVER) study (n = 1123) was conducted in Europe and Australia.
- The Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) study (n = 925) was conducted in North America.

The principal inclusion criteria were LV ejection fraction < 30%, New York Heart Association (NYHA) III-IV symptoms, and 6-minute walk ≤ 375 m (≤ 425 m if heart failure hospitalization within 6 months).

In RECOVER, patients were randomized to:

- etanercept 25 mg SC once weekly
- etanercept 25 mg SC twice weekly
- matching placebo.

In RENAISSANCE, patients were randomized to:

- etanercept 25 mg SC twice weekly
- etanercept 25 mg SC 3 times weekly
- matching placebo.

The primary endpoint within RECOVER and RENAISSANCE was the change in a recently developed composite clinical score[12] at 6 months. Follow-up was to continue after 6 months to capture mortality and morbidity data; the primary outcome for the entire RENEWAL program was the composite of death and heart failure hospitalization and the secondary outcome was all-cause mortality.

The studies were terminated prematurely due to a lack of benefit. Median follow-up was 5.7 months in RECOVER and 12.7 months in RENAISSANCE. The following results have not yet been published and should therefore be considered preliminary. In both RECOVER and RENAISSANCE, there were no significant differences between placebo and the 2 doses of etanercept in the number of patients who improved, were unchanged, or had a worsened composite clinical score ($P = 0.34$ and 0.17, respectively). For the entire RENEWAL program, the relative risk for combined death and heart failure hospitalization (2 doses of etanercept versus placebo) was 1.10 (95% CI, 0.91-1.33, $P = 0.33$). The relative risks for each dose are shown in Table 1. Again, no benefit of etanercept was discernable at any dose. Indeed, the point estimate appeared to favour placebo in RENAISSANCE where patients were exposed to etanercept for a longer period of time than in RECOVER.

The reasons for the lack of benefit for etanercept in patients with heart failure remain unclear. Potential mechanisms specific to etanercept include the possibility that the dimeric soluble TNF receptor can, under some circumstances, function simultaneously as TNF "carriers" (thus increasing serum level of TNF-α), in addition to being antagonists of TNF biologic activity.[13]

Infliximab in heart failure: The ATTACH study

A second approach to inhibit the actions of TNF-α was to use infliximab, a chimeric mouse/human IgG_1 monoclonal antibody to TNF-α that has a half-life of about 10 days.[14] In a recent pilot study (ATTACH), 150 patients with NYHA class III to IV heart failure and LV ejection fraction < 35% were randomized to:

Table 2: The ATTACH study – Principal results

		Placebo (n = 49)	Infliximab 5 mg/kg (n = 50)	Infliximab 10 mg/kg (n = 51)
Clinical Score				
Improved	Week 0-14	33%	38%	39%
	Week 14-28	43%	35%	37%
Unchanged	Week 0-14	59%	52%	39%
	Week 14-28	43%	48%	31%
Worse	Week 0-14	8%	10%	22%
	Week 14-28	14%	18%	31%
Change in EF (absolute)	Week 0-14	0.8±6	3.5±5.6†	2.1±6
	Week 14-28	3.4±8.1	4.2±7.1	1.3±6.9
Death/ Hospitalization	Week 0-14	2 (4%)	2 (4%)	8 (16%)
	Week 14-28	5 (10%)	4 (8%)	13 (25%)*

* p = 0.048
† p = 0.013 versus placebo
EF = left ventricular ejection fraction

- placebo (n = 49),
- infliximab 5 mg/kg (n = 50)
- infliximab 10 mg/kg (n = 51).

These doses were administered as a 2-hour intravenous infusion at weeks 0, 2, and 6. Assessments were conducted at week 14 and week 28. The primary endpoint was the clinical composite score at week 14. The secondary endpoints included the change in ejection fraction at week 14 and 28, and combined death and hospitalization for heart failure. The study was terminated prematurely because of the concern for harm. Unpublished preliminary results of the primary and secondary endpoints are summarized in Table 2. Neither dose of infliximab had any impact on the composite clinical score, the primary endpoint. LV ejection fraction was increased significantly compared to placebo at week 14 with infliximab at 5 mg/kg, but not at 10 mg/kg. At week 28, no benefit on ejection fraction was seen at either dose of infliximab, but the lack of benefit was most notable with the higher dose. At week 28, the risk of death and heart failure hospitalization was significantly greater in patients treated with the higher dose than for those treated with placebo (relative risk 2.84, 95% CI, 1.01 - 7.97, $P = 0.043$). A dose-dependent decrease in serum C-reactive protein (CRP) and IL-6 levels was nevertheless observed and was maintained at week 14. These preliminary results demonstrate that infliximab at 5 and 10 mg/kg has no effect on composite clinical score and the higher dose is associated with adverse clinical outcomes, despite apparent beneficial effects on the profile of serum markers for inflammation.

As with etanercept, the reasons for the lack of benefit with infliximab in patients with heart failure are unclear since there have been no published preclinical studies of the use of infliximab in chronic heart failure. Potential mechanisms that are specific to infliximab include a property of infliximab, (unlike etanercept) that binds to both soluble as well as transmembrane TNF. The latter binding effect may lead to complement-mediated cytotoxicity[15] that could account for the detrimental effect. Other explanations that apply equally to etanercept and infliximab include the concept that TNF-α induces cardiac hypertrophy and delays apoptosis;[16] therefore, this may play a protective role at a certain stage of the disease.[17] Regardless of the mechanisms, results of clinical studies to date indicate that specific targeting of TNF-α is unlikely to be the appropriate approach in the treatment of heart failure.

Broad spectrum approach to anti-inflammatory therapy

There are several potential explanations for failure of the targeted approach of anti-inflammatory therapy (eg, the use of etanercept and infliximab) to improve clinical outcomes in patients with advanced heart failure. First, targeted therapy, (ie, blocking the actions of TNF-α only) may be too selective since it does not address the issue of redundancy in the immune system. Other inflammatory cytokines that are upregulated and likely to play an equally important role in the pathogenesis of heart failure are essentially uninhibited. Second, the targeted approach does not lead to an upregulation of the potentially important modulating anti-inflammatory mediators such as IL-10. Accordingly, a broad-based approach to enhance the natural anti-inflammatory response without restricting targeting on the potential mediators may be more desirable. At present, there are 3 approaches of broad-based anti-inflammatory therapy that are under investigation:

- intravenous gamma-globulin (IVIG)
- immunoadsorption
- immune modulation therapy.

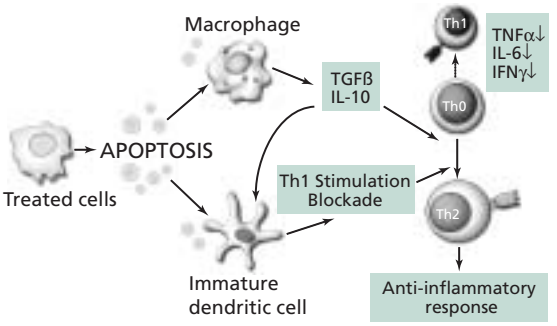
IVIG

Results of IVIG use in patients with heart failure have so far been mixed, with no benefit demonstrated in those with recent-onset dilated cardiomyopathy,[18] and an increase in ejection fraction reported in patients with chronic heart failure.[19]

Immunoadsorption

Immunoadsorption is a technique that is supposed to remove specific antibodies from the circulation. In a small German study of 34 patients with dilated cardiomyopathy

Figure 1: Immune response to apoptosis



and high serum anti-ß$_1$ antibodies, during 5 consecutive days, immunoadsoprtion was accompanied by an improvement in ejection fraction and a striking reduction in LV volumes.[20] It is unclear, however, whether this improvement was due to the removal of anti-ß$_1$ antibodies or other nonspecific mechanisms.

Immune modulation therapy in chronic heart failure

Immune modulation therapy (IMT) represents a novel nonpharmacological approach to anti-inflammatory therapy that involves removing blood from the patient, followed by *ex-vivo* treatment with a variety of stressors that lead to apoptotic cell death. The treated blood cells are then administered intramuscularly to the patient to modulate the immune response. The proposed mechanism of action for IMT is shown in Figure 1. The uptake of apoptotic cells into macrophages results in a downregulation of proinflammatory cytokines (including TNF-α, IL-1ß, and IL-8), accompanied by enhanced production of the anti-inflammatory cytokines (TGF-ß and IL-10).[21,22] IL-10 redirects the immune responses towards a T-helper 2 (Th2) pathway. This dampens the inflammation caused by Th1 cells by suppressing the production of proinflammatory cytokines and inhibiting chemotaxis.[23,24] Dendritic cells are bone marrow-derived cells that are capable of capturing and presenting antigens to T cells. Interestingly, phagocytosis by dendritic cells of necrotic cells or transformed cell lines induces a proinflammatory Th1 response. By contrast, phagocytosis of apoptotic cells directs the cells to an anti-inflammatory Th2 response. Animal studies have demonstrated that IMT reduces allergic contact sensitivity,[25] atherosclerosis,[26] renal ischemia/reperfusion injury,[27] and reduces proinflammatory cytokines, while increasing anti-inflammatory cytokines.[28] Clinical studies have demonstrated that IMT improves microvascular endothelial function in patients with Raynaud's syndrome,[29] and improves walking distance in patients with peripheral vascular disease.[30]

Table 3: Immune modulatory therapy in heart failure: Baseline data

	Active (n = 36)	Placebo (n = 37)
Age (years)	63	60
Male/female	25/11	25/12
Caucasians/blacks/others (%)	70/27/3	68/24/8
NYHA class III/IV	36/0	36/1
Diabetes	16	9
Ejection fraction (%)	23±8	22±8
ACE inhibitors or angiotensin receptor blockers	32	33
Digitalis	30	31
ß-blockers	20	18
Spironolactone	15	19

Clinical data on the use of IMT in heart failure

A feasibility study on the use of IMT was recently completed in 73 patients with severe heart failure. In this multicentre study, patients with heart failure and NYHA III/IV symptoms were randomized to active treatment (n = 36) or placebo (n = 37). IMT consisted of an outpatient procedure that included:

- collection of 10 mL sample of citrated blood
- *ex-vivo* exposure to oxidative stress at increased temperature, and
- intramuscular injection of treated autologous blood.

The treatment was administered on day 1, 2, and 14, and then once-a-month thereafter for 6 months and 8 injections in total. The key inclusion criteria included NYHA class III/IV symptoms, ejection fraction <40%, 6-minute walk distance <300 m, and optimal background medical therapy. The protocol-specified primary endpoints were the 6-minute walk distance and NYHA functional class. The secondary endpoints were all-cause mortality, all-cause hospitalization, LV ejection fraction, and quality of life.

The results of the study were recently presented at the Heart Failure Society of America and the American Heart Association meetings.[31] The findings presented in this *Cardiology Scientific Update* are not yet published and therefore should be considered preliminary and subject to revision. In brief, as shown in Table 3, at baseline the active treatment and placebo groups were comparable in

Table 4: Immune modulatory therapy in heart failure – protocol pre-specified secondary outcomes

	Active (n = 36)	Placebo (n = 37)	P-value
Death	1	7	0.022
Hospitalization	12	21	0.008
Change in MLHF	-12.2	-4.5	0.110

MLHF = Minnesota Living with Heart Failure Score

age, gender, race, NYHA class, and LV function. The use of medication reflects optimal pharmacologic therapy. For the primary endpoints, the change in the 6-minute walk distance at baseline and 6 months, respectively, was not different in the 2 treatment groups ($P = 0.57$). There were also no significant differences in the percent of patients with improved NYHA class ($P = 0.14$). Results of the secondary outcomes are shown in Table 4. Survival analysis demonstrated that IMT significantly reduced the risk of death as well as all-cause hospitalization. The composite endpoint of all-cause mortality and all-cause hospitalization was significantly reduced (12 versus 22 events, $P = 0.005$). There was a trend for improved quality of life as measured by the Minnesota Living with Heart Failure Score. LV ejection fraction increased only slightly in both groups (22.8% to 23.5% in active, 21.5% to 22.7% in placebo).

Several exploratory analyses were also conducted. Eleven and 4 patients in the active and placebo groups, respectively, reported an improvement ($P = 0.046$), 13 and 9 patients, respectively, reported no change (NS), whereas 12 and 24 patients, respectively, reported worsening ($P = 0.01$) in a prespecified clinical composite score. The changes from baseline in plasma levels of IFNγ, TNF-α, IL-10, IL-6, CRP, and brain natriuretic peptide were surprising and not significantly different between the 2 groups, although it is difficult to draw conclusions from plasma data. Heart rate-corrected QT interval (QTc) and temporal dispersion of QT interval (QTd) were measured in 20 and 15 patients in the active and placebo groups, respectively.[32] The 2 parameters were comparable at baseline in the 2 groups. However, QTc decreased by a mean of 18 msec in the active group and increased by 12 msec in the placebo group ($P = 0.035$). Similarly, QTd decreased by 16 msec in the active group, but increased by 19 msec in the placebo group ($P = 0.035$). A list of adverse events is shown in Table 5. Systemic adverse events as well as those related to injection sites were uncommon and IMT appears to be very well tolerated.

Table 5: Immune modulatory therapy in heart failure – adverse events

	Active (n = 36)	Placebo (n = 37)
Hypotension	5	4
Worsening heart failure	9	27
Arrhythmias	3	1
Renal failure	2	1
Chest pain/Angina	15	22
Infection	29	32
Injection site (number of injections)	290	256
Pain	9	3
Edema	1	0
Bruising	2	1
Paresthesia	0	1

Summary

There is no doubt that immune activation plays an important role in the pathophysiology of heart failure. As a result, next to neurohormonal inhibition, modulation of the immune system could potentially be the next breakthrough in heart failure therapy. Clinical studies to date, however, have revealed that investigators have been too optimistic in anticipating that targeting one cytokine in the inflammatory cascade would lead to clinical benefits. A broad-based approach to anti-inflammatory therapy such as IMT is theoretically more attractive and the results of the feasibility study of IMT presented in this *Cardiology Scientific Update* are thus far encouraging. However, it should be cautioned that the feasibility study was not designed to assess clinical outcomes and the favourable effects on mortality and hospitalization demonstrated in this study need to be confirmed in a large study primarily designed to study clinical outcomes. In this regard, a large-scale phase III trial – A MultiCenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study to Assess the Effects of Immune Modulation Therapy (IMT) on Mortality and Morbidity In Patients with Chronic Heart Failure (ACCLAIM) Study – will soon be underway.

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