Novel Therapies for Heart Failure
– Where Do They Stand? –

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Despite advances in therapy, patients with heart failure (HF) continue to experience unacceptably high rates of hospitalization and death, as well as poor quality of life. As a consequence, there is an urgent need for new treatments that can improve the clinical course of the growing worldwide population of HF patients. Serelaxin and ularitide, both based on naturally occurring peptides, have potent vasodilatory as well as other effects on the heart and kidneys. For both agents, phase 3 studies that are designed to determine whether they improve outcomes in patients with acute HF have completed enrollment. TRV027, a biased ligand for the type 1 angiotensin receptor with effects that extend beyond traditional angiotensin-receptor blockers is also being studied in the acute HF population. Omecamtiv mecarbil, an inotropic agent that improves myocardial contractility by a novel mechanism, and vericiguat, a drug that stimulates soluble guanylate cyclase, are both being developed to treat patients with chronic HF. Finally, despite the negative results of the CUPID study, gene transfer therapy continues to be explored as a means of improving the function of the failing heart. The basis for the use of these drugs and their current status in clinical trials are discussed. (Circ J 2016; 80: 1882–1891)

Key Words: Gene transfer; Heart failure; Novel therapies

Heart failure (HF) is a common, costly and growing medical problem around the world. In the USA, an estimated 6 million patients suffer from HF and that number is expected to grow to over 8 million by 2030. The global prevalence of HF exceeds 25 million patients and growth commensurate with that anticipated in the USA is likely. The overall cost of HF to healthcare systems is staggering. In the USA, over 30 billion dollars is spent annually for the care of HF patients and this amount will increase substantially as prevalence rises. Along with the monetary cost, HF exacts an enormous human toll; patients are hospitalized frequently and quality of life (for both patients and their families) is amongst the lowest for chronic diseases. Most importantly, life expectancy is greatly impaired.

Insights into the basic pathophysiology of HF have evolved over the past several decades. As summarized in Figure 1, this has resulted in substantial changes in therapy. In the 1970s, HF was viewed as a condition in which poor cardiac pump function and fluid retention caused organ hypoperfusion and congestion. Based on this paradigm, treatment was directed towards augmenting myocardial contractility using digitalis glycosides and relieving volume overload with diuretics. During the 1960s and 1970s, the influence of the peripheral circulation on cardiac performance was recognized and vasodilator drugs that reduce the load on the heart were added to the therapeutic regimen. Further progress was made when investigators found that the benefits of angiotensin-converting enzyme inhibitors (ACEIs) were related predominantly to their ability to inhibit maladaptive cardiac remodeling. Subsequent studies assessing additional approaches to block neurohormonal activation demonstrated that angiotensin-receptor blockers (ARBs), β-blockers and mineralocorticoid-receptor antagonists also substantially improved outcomes in HF patients. As a result, neurohormonal blocking agents emerged as cornerstones of therapy.

Despite advances in therapy, the clinical course of HF patients remains highly unfavorable and new approaches to improving outcomes are needed. Although therapeutic strategies that modulate neurohormones continue to evolve, as evidenced by recent success with combined neprilysin and angiotensin (Ang) inhibition, further advances will likely be based on targeting novel pathways in the failing heart. The focus of this review is presenting the rationale for several new approaches and to summarize where they stand in the course of their development. Although new agents can be categorized in a variety of ways, they are separated in this review according to whether they are being developed to treat acute or chronic HF (AHF/CHF).

New Drugs for Treating AHF

Given the growing prevalence of HF, it is not surprising that hospitalization rates for AHF are quite high. Although in-hospital mortality rates have decreased over the past several decades, high rates of readmission and post-discharge death...
Serelaxin (recombinant human relaxin-2)

Relaxin-2, a naturally occurring peptide, is present at low levels in both males and females. It binds to relaxin family peptide receptors (RXFPs) primarily in the cardiovascular system and kidneys. Relaxin levels are increased in the circulation of pregnant females where it appears to play an important role in many of the cardiovascular adaptations that occur. Serelaxin, a recombinant form of the human relaxin molecule, has an identical structure, similar receptor affinities and downstream signaling as the naturally occurring peptide. Relaxin/serelaxin vasodilatory effects are mediated through a G-protein coupled pathway that leads to activation of nitric oxide (NO) synthase and NO production. Other effects include activation of the VEGF pathway, matrix metalloproteinases, endothelin receptors and changes in the extracellular matrix of blood vessel walls. The effects of relaxin are depicted in Figure 2. Based on results seen in early studies, a clinical trial program with serelaxin in AHF was initiated.

In the phase II pre-RELAX-AHF (RELAXin for the treatment of patients with Acute Heart Failure) study, 234 AHF patients were randomly assigned to either placebo or serelaxin at doses ranging from 10, 30, 100 to 250 μg/kg/day in addition to standard therapy. Patients were enrolled regardless of their baseline ejection fraction (EF), but were required to have a systolic blood pressure (SBP) >125 mmHg and an estimated glomerular filtration rate between 30 and 75 ml/min/1.73 m². The greatest improvement in signs and symptoms of congestion occurred with the 30 μg/kg/day dose. Reductions in cardiovascular death and readmission for HF or renal failure at day 60 after discharge were also seen with serelaxin.

The phase 3 RELAX-AHF (RELAXin in Acute Heart Failure) trial randomized 1,161 patients hospitalized for AHF. Entry into the study required the presence of symptomatic dyspnea, evidence of congestion, mild-moderate renal insufficiency and persist. Remarkably, no currently available drug has been shown to favorably affect post-discharge outcomes. Thus, there is a major unmet need for finding new therapeutic approaches for managing AHF episodes.

Figure 2. Mechanism of serelaxin action. ETα receptor, endothelin receptor type B; ET-1, endothelin-1; MMP, matrix metalloproteinase; NO, nitric oxide; NOS, nitric oxide synthase; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor. (Reprinted from Reference 12 with permission.)
a SBP >125mmHg. Randomized patients received either a 48-h infusion of placebo or serelaxin (30μg/kg/day) in addition to standard therapy. Overall, serelaxin had a significant effect on the visual analog score (VAS) over the first 5 days after enrollment. The improvement in the VAS score was related to a reduction in episodes of worsening HF (WHF) that required intensification of therapy. Signs and symptoms of congestion were also improved with serelaxin and length of hospital (and critical care unit) stay was reduced. Although readmission rates were not significantly affected, serelaxin treatment was associated with significant (37%) reductions in both cardiovascular and all-cause death at 180 days, a finding that replicated the results of the pre-RELAX-AHF study (Figure 3). The reduction in mortality rate with serelaxin was seen in patients with ischemic or non-ischemic etiologies of HF, and they occurred regardless of whether the patient had preserved or impaired systolic function. A possible explanation for how a 48-h infusion of serelaxin improved 180-day survival is that more rapid decongestion with the drug during the acute episode helped protect vital organs (eg, heart and kidney) from further damage during a period of high vulnerability. Evidence that biomarkers indicative of organ injury were reduced by serelaxin treatment supports this possibility.

The ongoing ~6,800-patient RELAX-AHF2 study is designed to confirm the reductions in deaths and WHF seen in RELAX-AHF. Recruitment into this international trial is complete and the results will be available in early 2017.

**Ularitide**

This peptide is the synthetic form of the naturally occurring urodilatin molecule, which belongs to the natriuretic peptide family, a group of hormone/paracrine factors with natriuretic, diuretic, vasodilatory and other properties that are potentially beneficial in HF. Urodilatin, a 32-amino acid-containing peptide with the same sequence and structure as the 28-amino acid-containing atrial natriuretic peptide (ANP), except for the addition of 4 amino acids at the N-terminal extension, is generated through differential processing of pro-ANP in the distal renal tubule cells. Upon secretion into the urine, urodi-latin binds to natriuretic peptide type A receptors in the inner medullary collecting duct and activates intracellular guanylate cyclase, which leads to an increase in cyclic guanosine monophosphate (cGMP) and downstream cGMP-dependent protein kinases. As shown in Figure 4, urodilatin regulates water and sodium reabsorption by the collecting duct. Administration of urodilatin to healthy volunteers and HF patients provided evidence supporting further testing of the synthetic peptide in HF patients.

SIRIUS I (Safety and efficacy of an Intravenous placebo-controlled Randomized Infusion of Ularitide in a prospective double-blind Study in patients with symptomatic, decompensated CHF) assessed ascending doses of ularitide in 24 patients hospitalized for HF. Overall, there were improvements in hemodynamics and biomarkers at higher doses of ularitide. SIRIUS II randomized 221 patients with AHF to doses of ularitide ranging between 7.5 and 30 ng/kg/min. After 6h of therapy, all groups receiving ularitide experienced reductions in pulmonary artery wedge pressure compared with both their baseline levels and placebo treatment. At higher doses, there were reductions in systemic vascular resistance (SVR) and increases in cardiac index compared with baseline levels. Patients who received ularitide experienced a significant improvement in dyspnea on the 7-point Likert scale compared with their own baseline levels and placebo changes. There were significant reductions in NT-proBNP levels with higher doses of ularitide at 24h and trends towards reduction in deaths with all doses of ularitide compared with placebo both in-hospital and post-discharge.

In the phase 3 TRUE-AHF (Trial of Ularitide’s Efficacy and safety in patients with Acute Heart Failure: NCT01661634) over 4,300 patients worldwide were randomized to receive either 15ng/kg/min of ularitide or placebo in addition to standard medical therapy. The co-primary endpoints are: (1) improvement in a hierarchical clinical composite comprised of elements associated with patient global assessment using a 7-point scale; persistent or WHF requiring an intervention (initiation or intensification of IV therapy, circulatory, or ventilator mechanical support, surgical intervention, ultrafiltration, hemofiltration or dialysis); and all-cause death, and (2) freedom from cardiovascular death during follow-up after randomization for the entire duration of the trial. The trial has been completed and results are expected in late 2016.

**TRV027: a Biased Ligand**

Most of the recognized effects of Ang II are initiated by an interaction of the peptide with its type 1 (AT1) receptor. Vasconstriction and other downstream effects attributed to the AT1 receptor depend on G-protein pathways. However, additional AT1 receptor signaling pathways involving β-arrestin-1 and -2 exist. Signaling through these alternative pathways desensitizes G-protein signals, promotes receptor internalization and stimulates mitogen-activated protein kinase and phosphoinositide 3-kinases. TRV027, a novel AT1 receptor-biased ligand, simultaneously competitively antagonizes Ang II-stimulated G-protein signaling while stimulating the β-arrestin pathway. This approach is designed to block Ang II effects such as vasoconstriction and cardiac hypertrophy while enhancing beneficial effects on myocardial contractility, AT1 receptor desensitization and internalization, and activation of anti-apoptotic pathways. When TRV027 was compared with the ARBs, losartan and telmisartan, both classes of drug lowered BP, but only the biased ligand increased myocardial contractility. In a canine model, TRV027 decreased PCWP and both systemic and renal vascular resistances, while
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ARB has been shown to be superior to an ACEI in improving HF outcomes and this approach has been given a strong recommendation in the recent guidelines. Ibrabradine, a drug that slows heart rate by acting on the If channels in the sinoatrial node, has also recently been recommended in the guidelines for treating symptomatic patients with HF and reduced EF (HFrEF) who are in normal sinus rhythm with a heart rate >70 beats/min. Nevertheless, outcomes remain poor for HFrEF patients and additional effective treatments are needed.

Omecamtiv Mecarbil

Past attempts at improving myocardial contractility in HF patients have either failed to show benefits, provided evidence of clinical improvement that were offset by worrisome side effects or proved to be harmful. The poor outcomes associated with these agents is related to the fact that all of them increase intracellular calcium levels in cardiomyocytes so that augmentation of contractility comes at the cost of increasing myocardial oxygen consumption (MVO₂).

Omecamtiv mecarbil is a cardiac myosin activator that binds directly to the myosin catalytic domain. It stabilizes an increasing cardiac output and renal blood flow.

Initial studies in humans demonstrated that TRV027 had a short half-life and was well tolerated. No safety concerns emerged in normal subjects or patients. Not surprisingly, high plasma renin levels were associated with the greatest reduction in BP. In the phase 2b BLAST-HF (Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure) trial, 500 AHF patients with SBP between 120 and 200mmHg were randomized within 24h of initial presentation to 1, 5, or 25mg/h of TRV027 or to placebo in a 1:1:1:1 ratio. Endpoints included rehospitalization or death at 30 days, WHF at day 5, length of hospitalization and change in the dyspnea VAS. In May 2016, a preliminary press release by the sponsor stated that TRV027 failed to meet either the primary or secondary endpoints in BLAST-HF. More in-depth descriptions of these results are anticipated and at this time it is uncertain whether there will be further studies of TRV027 in HF.

New Drugs for Treating HF

There have been important advances in the treatment of patients with HF. The combination of neprilysin inhibition with an increasing cardiac output and renal blood flow. Initial studies in humans demonstrated that TRV027 had a short half-life and was well tolerated. No safety concerns emerged in normal subjects or patients. Not surprisingly, high plasma renin levels were associated with the greatest reduction in BP. In the phase 2b BLAST-HF (Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure) trial, 500 AHF patients with SBP between 120 and 200mmHg were randomized within 24h of initial presentation to 1, 5, or 25mg/h of TRV027 or to placebo in a 1:1:1:1 ratio. Endpoints included rehospitalization or death at 30 days, WHF at day 5, length of hospitalization and change in the dyspnea VAS. In May 2016, a preliminary press release by the sponsor stated that TRV027 failed to meet either the primary or secondary endpoints in BLAST-HF. More in-depth descriptions of these results are anticipated and at this time it is uncertain whether there will be further studies of TRV027 in HF.

Figure 4. Schematic of the role of urodilatin under physiological and pathophysiological conditions. (A) Nephron highlighting distal tubule (synthesis site of urodilatin) and collecting duct (binding site of urodilatin). (B) Sodium concentration as stimulus for synthesis of urodilatin in distal tubule cells and excretion into the urine, mediated by transduction mechanisms (C) and binding to NPR-A receptor in the inner medullary collecting duct. (C) Processing of urodilatin from pro-ANP. Enzyme responsible not known yet (aa, amino acids). AC, adenylyl cyclase; ANP, atrial natriuretic peptide; PKC, protein kinase. (Reprinted from Reference 27 with permission.)
Figure 5. Sites of action in cardiomyocytes of currently available inotropic agents and of omecamtiv mecarbil. Unlike other inotropic agents, omecamtiv mecarbil does not increase calcium levels in cardiomyocytes. It acts directly on the myosin catalytic domain to stabilize an actin-bound conformation of myosin and it increases the entry rate of myosin into the tightly bound force producing state with actin. (Reprinted from Reference 48 with permission.)

actin-bound conformation of myosin and increases the entry rate of myosin into the tightly bound force producing state with actin. As summarized in Figure 5, the net effect is to increase cardiomyocyte fractional shortening without increasing Ca$^{2+}$ transients or MVO$_2$. In a canine model, omecamtiv mecarbil improved measures of systolic function, including wall thickening, fractional shortening, stroke volume and cardiac output. These changes were associated with an increase in systolic ejection time (SET). In contrast to dobutamine, a β-agonist, omecamtiv mecarbil did not increase the rate of left ventricular (LV) pressure development. Myocardial energetics with omecamtiv mecarbil were unchanged and there was no increase in MVO$_2$.

In healthy volunteers, omecamtiv mecarbil increases SET, stroke volume and % fractional shortening in a dose-dependent manner. A subsequent phase 2 study in 45 stable HF patients demonstrated placebo-corrected, concentration increases in LV ejection time and stroke volume. Higher plasma concentrations significantly reduced LV end-diastolic and end-systolic volumes. Of concern, however, was evidence of cardiac ischemia at high plasma concentrations of the drug, likely caused by excessive SET prolongation that reduced coronary blood flow as diastole became progressively truncated.

To determine the potential risk of prolonging systole in HF patients, the safety and tolerability of omecamtiv mecarbil was studied in patients with ischemic cardiomyopathy and a history of angina, a population that would be particularly vulnerable to a reduction in coronary blood flow. Patients received intravenous drug or placebo over 20h in escalating doses to achieve plasma concentrations known to increase systolic function but at levels below those previously shown to precipitate ischemia. After an exercise treadmill test during the final 2h of drug infusion, patients entered an oral dosing period for 7 additional days. The results showed that omecamtiv was well tolerated during exercise without any indication of increased likelihood of myocardial ischemia even when MVO$_2$ was increased during exercise.

In the phase 2 ATOMIC-HF (Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) study, the pharmacokinetics, pharmacodynamics, tolerability, safety, and efficacy of omecamtiv mecarbil were assessed in 606 HFrEF patients during an episode of AHF. Patients were randomly assigned to receive a 48-h intravenous infusion of placebo or drug in 3 sequential, escalating-dose cohorts. There were plasma concentration-related increases in LV SET (P<0.0001) and decreases in end-systolic dimension (P=0.05) with omecamtiv mecarbil. Although omecamtiv mecarbil did not improve the primary endpoint of dyspnea relief, a prespecified secondary analysis showed greater dyspnea relief at 48h (placebo, 37% vs. omecamtiv mecarbil, 51%; P=0.034) and through 5 days (P=0.038) in the high-dose cohort. Safety and tolerability were good and there was no evidence of an increase in ventricular or supraventricular tachyarrhythmias. Small increases in plasma troponin concentrations were seen in patients treated with omecamtiv mecarbil compared with placebo, but there was no obvious relationship with drug concentration.

The phase 2 COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure; NCT01786512) trial was designed to select an oral formulation and dose of omecamtiv mecarbil for chronic dosing in HFrEF patients and to characterize pharmacokinetics over 20 weeks of treatment. Secondary objectives were to assess safety and tolerability, changes from baseline in SET, stroke volume, LV end-diastolic diameter and NT-proBNP levels. Patients received either 25mg bid, 25mg bid increased to 50mg bid based on pharmacokinetic determinations or placebo. The latter group was included to determine if a pharmacokinetic-based strategy could be used to achieve effective drug levels while avoiding levels that would excessively prolong SET. The results showed that pharmacokinetic-based dose titration successfully controlled patient exposure to the drug. In addition, omecamtiv mecarbil increased SET, stroke volume and LV ejection while it tended to reduce LV volumes and dimensions. There were also reductions in heart rate and NT-proBNP levels. Small troponin I increases occurred with omecamtiv mecarbil, but there was no increase in cardiac adverse events. Overall, adverse events and serious adverse events did not differ from placebo. A phase 3 study with omecamtiv mecarbil to assess clinical efficacy as well as safety in a larger patient is antici-
pated to be initiated in the near future.

**Soluble Guanylate Cyclase (sGC) Activation**

Endothelial cells (ECs) play a critical role in regulating adaptation of the heart, kidneys, and circulatory system to changes that occur during health and disease by releasing factors that influence both the growth and tone of underlying vascular smooth muscle cells. NO is a key mediator of these EC effects. Release of NO from ECs activates sGC, leading to an increase in the production of cGMP. Downstream effects of this cyclic nucleotide include inhibition of inositol 1,4,5-trisphosphate, stimulation of calcium pump mechanisms, and inhibition of voltage-gated cardiac calcium channels. The net effect is a reduction in intracellular calcium concentration and vasomotor tone. However, in HF, NO availability is compromised by both diminished production caused by EC dysfunction and increased breakdown by reactive oxygen species and this leads to a reduction in cGMP generation.

Agents that stimulate or activate sGC directly offer a novel strategy for increasing cGMP levels that does not depend on NO availability. Riociguat, a sGC stimulator already approved by the US FDA for treating chronic thromboembolic pulmonary hypertension and pulmonary artery hypertension, was studied in HF patients in the LEPHT (Left Ventricular systolic dysfunction associated with Pulmonary Hypertension riociguat Trial) study. This phase 2 study enrolled 201 symptomatic HFpEF with pulmonary hypertension (mean PAP ≥25 mmHg at rest). Patients were randomly assigned in a double-blinded fashion to receive 0.5, 1.0, or 2.0 mg t.i.d. of riociguat or placebo over 16 weeks. Although riociguat failed to achieve its primary endpoint of significantly reducing mPAP compared with placebo, it did significantly increase the cardiac index and decrease both SVR and PVR compared with placebo. At the highest dose, riociguat improved measures of quality of life and 6-min walk distance. Riociguat was well tolerated. Discontinuation of treatment was similar between study groups, although hypotension was a dose-limiting side effect.

The SOCRATES (SOluble guanylate Cyclase stimulatoR in heArT failurE Studies) program assessed the effects of vericiguat, a once-daily oral sGC stimulator, in HFpEF patients (SOCRATES-REDUCED) or preserved EF (SOCRATES-PRESERVED). In SOCRATES-REDUCED, the primary objective was to characterize in clinically stable but symptomatic patients, the tolerability, pharmacodynamics effects and pharmacokinetics of vericiguat and to determine if there was a significant dose-effect of vericiguat on NT-proBNP at 12 weeks. Exploratory endpoints included clinical outcomes (i.e., cardiovascular death and HF hospitalization) and echocardiographic parameters of LV structure and function. Patients were randomized to receive 1.25, 2.5, 5, or 10 mg of vericiguat or placebo. The study failed to meet its primary efficacy endpoint of a significant reduction in NT-proBNP for the pooled 2.5/5/10 mg dose groups compared with placebo. Exploratory analyses, however, demonstrated a significant dose-response relationship, as well as greater NT-proBNP reduction with the 10-mg dose than with placebo (Figure 6). The 10-mg dose was associated with a significantly greater increase in LVEF than placebo (3.7 units vs. 1.5 units; P<0.05) and with a trend towards reductions in clinical events. There were no significant effects of vericiguat on BP, heart rate, renal function or troponin. A phase 3 study with vericiguat is being planned.

**Gene Transfer (GT) Therapy**

GT therapy for HF involves introducing recombinant human genetic material to a patient in order to alter levels of a protein that will directly or indirectly (e.g., paracrine or systemic effects) improve cardiac function. Although a variety of vectors can be used, viruses are preferred by most investigators. Adeno-associated viruses (AAVs), which are minimally immunogenic, do not integrate into the patient’s own genome, are not cell cycle-dependent and have the capability for long-term transgene expression, are of particular interest. Delivery methods include antegrade coronary perfusion, retrograde perfusion through the coronary sinus, direct injection into either the epicardium (during heart surgery) or into the endocardium (using catheter-based techniques) and seeding in the pericardium. Limitations of AAVs include insert capacity and the presence of neutralizing antibodies (NAbs) that inhibit uptake of the virus into cells in many patients. Of 1,552 patients who were screened for NAbs in a recent study, nearly 60% had titers that would interfere with successful gene delivery. The likelihood of having high titers of NAbs increased with age, but no clear-cut geographic pattern was noted.

Potential targets for GT therapy in the failing heart include adrenergic signaling, calcium handling, diastolic function, cell survival, angiogenesis, stem cell recruitment and monogenetic causes of cardiomyopathy. Abnormalities in calcium handling have drawn considerable attention. Sarcoendoplasmic reticulum calcium ATPase (SERCA2a) is an enzyme that plays a critical role in regulating calcium fluxes within cardiomyocytes. SERCA2a activity is reduced in HF, resulting in reduced calcium reuptake by the sarcoplasmic reticulum (SR) during diastole and less calcium available in the SR for release during systole. Thus, diminished SERCA2a activity adversely affects both myocardial relaxation and contraction. In cardiomyocytes isolated from HF patients, increasing SERCA2a activity by GT improved contractile and relaxation properties. In both small and large animal models, an AAV1/ SERCA2a construct improved global cardiac function. A small pilot dose-finding study, the CUPID 1 Trial (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease), reported that a 4013 DNase-resistant particles dose of AAV1/SERCA2a was well tolerated and that it improved measures of patient well-being and HF severity. Clinical events were markedly reduced compared with a pl-
were found to be at the lower end of the threshold for dose-response curves in pharmacology studies, suggesting that only a small proportion of cardiomyocytes were expressing AAV1-delivered SERCA2a.

In CUPID 2, AAV1/SERCA2a was delivered by antegrade intracoronary infusion and perhaps better results could have been obtained if retrograde perfusion or direct injection had been used. A higher dose of AAV1/SERCA2a might also have resulted in more robust transgene expression. Another possibility is that changes in the manufacture of AAV1/SERCA2a from CUPID 1 to CUPID 2 that resulted in a reduced number of empty AAV viral capsid particles used in the second study adversely affected transduction efficiency. There is evidence that in addition to the number of DNA-containing viral particles (which was equivalent in both CUPID studies), the total number of particles is important for in-vivo activity because empty capsids might serve as decoys to engage NAbs and possibly other interfering factors present in the patient’s serum.

Future studies will need to carefully consider method of delivery, dose, total number of capsids and interactions between the vector and the patient’s serum in order to optimize GT efficiency.

Despite the failure of CUPID 2, the possibility that augment-
ing SERCA2a activity will benefit HF patients is being studied using other vectors and modes of delivery. Alternative methods for increasing SERCA2a activity including the use of molecules that target the small ubiquitin-like modifier type 1 (SUMO 1), which regulates SERCA2a in cardiomyocytes, are also being investigated. Another potential use of SERCA2a GT is in treating pulmonary hypertension. There is evidence from a large animal model that intratracheal delivery of AAV1/SERC2a ameliorates chronic post-capillary pulmonary hypertension.

Other targets for GT include adrenergic signaling and there is evidence that overexpression of adenyl cyclase improves β-adrenergic responsiveness. In a phase 2 study, the safety and efficacy of intracoronary delivery of adenosine 5'-encoding adenyl cyclase 6 (Ad5.hAC6) was evaluated in 56 HFpEF patients who received ~10^7–10^12 Ad5.hAC6 3.2 Å-virus particles or placebo in addition to their standard therapy. Patients were followed for up to 1 year. Although there were no significant differences in exercise duration at 4 and 12 weeks between the high-dose and placebo groups, there was an increase in EF of 6.0 units in the high-dose groups at 4 weeks but not at 12 weeks. AC6 GT increased basal LV peak–dP/dt at 4 weeks. Ad5.hAC6-treated patients also demonstrated a trend towards reduced number of hospitalizations.

GT to increase expression of stromal cell-derived factor-1 (SDF-1) has also been tested in patients with ischemic cardiomyopathy. This strategy is based on evidence showing that SDF-1 is a key regulator of tissue repair and that it induces homing of bone marrow–derived and cardiac stem cells to the site of ischemic injury, inhibits cardiomyocyte death and has favorable effects on remodeling. In a PHASE 2 study, 93 HFpEF patients with ischemic disease received intramyocardial injection of a single treatment of 15 or 30 mg of placebo or SDF-1 (pSDF-1) or placebo. Although a primary composite endpoint was not met, there was a trend towards improved EF with pSDF-1. Patients in the lowest EF tertile who received 30 mg of drug demonstrated significant placebo adjusted changes in EF after 12 months. There were also trends towards reduced LV volumes and NT-proBNP levels with pSDF-1 treatment. There were no anticipated serious product-related adverse events. Studies in larger groups of patients to determine effects on remodeling and the benefits of repeated administration are currently in the planning stage.

Conclusions

Despite efforts at prevention and an increasing number of treatment options, HF remains a major public health problem worldwide. Strategies to treat HF have evolved in parallel with insights into underlying pathophysiologic mechanisms. Although the neurohumoral paradigm for understanding HF has given rise to several agents that have greatly altered the clinical course of patients, it is likely that further advances will come from approaches that use novel approaches to target fundamental derangements in cardiac cells that cause HF to occur.

References

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