Novel Therapies Take Aim at Heart Failure

Possible immunoregulatory treatments include plasmapheresis and immunoglobulin infusions.

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ORLANDO — Cardiologists on the lookout for badly needed novel treatments for heart failure continue to have high hopes for immunoregulatory therapies, even after anti–tumor necrosis factor biologics were ineffective in large randomized trials. Cardiologists now think they understand why anti-TNF therapy failed. They are focusing on developing more nonspecific, broad-spectrum anti-inflammatory/immunologic strategies.

Among the approaches showing early clinical promise are plasmapheresis, intravenous immunoglobulin infusions, nonpharmacologic immune modulation therapy aimed at harnessing cell apoptosis to decrease chronic inflammation, extracorporeal immunoabsorption of cardiac autoantibodies, and statin therapy.

"We're perhaps on to something here with immune modulation and heart failure. We have to define the patient population for whom this will be most beneficial, but we seem to be inching ever so slowly toward that conclusion," Kenneth L. Baughman, M.D., said at a symposium on novel therapies for heart failure held during the annual meeting of the American College of Cardiology.

But immunologic therapies aren't the only favorable prospect on the horizon for heart failure. Speakers also described a novel drug class—the vasopressin antagonists—that shows considerable promise, as does erythropoietin for correcting the anemia that often accompanies heart failure.

Many observers were surprised when etanercept (Enbrel) failed to improve symptoms or survival in major clinical trials totaling roughly 1,500 heart failure patients. In hindsight, the drawback of anti-TNF therapy for heart failure may have been its very specificity. Solid evidence indicates that all elements of the inflammatory cascade are involved in the progression of heart failure, including not only proinflammatory cytokines such as TNF, but also activated B and T cells, antimyocardial antibodies, peripheral monocytes, and the complement system.

"Elimination of the biologic activity of one proinflammatory cytokine alone may not be enough," observed Guillermo Torre-Amione, M.D., Ph.D., medical director of the cardiac transplant service at the Methodist DeBakey Heart Center, Houston.

Dr. Baughman said broadly immunosuppressive agents such as prednisone and azathioprine have shown good efficacy in recent placebo-controlled trials in patients with cardiomyopathy of at least 6 months' duration. Responders had no viral presence on pretreatment myocardial biopsies but had antibodies directed against the heart.

"This indicates viral persistence is a bad thing and having antibodies or being in a state of immune activation is a good thing if you're treating with immunosuppressives," said Dr. Baughman, professor of medicine at Harvard Medical School and director of the advanced heart disease section at Brigham and Women's Hospital, Boston.

Dr. Torre-Amione noted that although nonspecific immunoregulatory therapies such as plasmapheresis and immunoabsorption are unfamiliar to cardiologists, these therapies are scoring successes in other fields, particularly for autoimmune and neuroinflammatory diseases. He and Dr. Baughman reviewed the status of these novel therapies in heart failure:

▶ **Plasmapheresis.** This involves removing patient's plasma from withdrawn blood, then retransfusing the formed elements. The regimen typically involves five to seven cycles of plasmapheresis, with or without intravenous immunoglobulin (IVIG) infusions to enhance the anti-inflammatory effect. The mechanism of action remains unclear.

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"No one really knows how plasmapheresis works. The more I look, the less I understand," Dr. Torre-Amione said. "But clearly there are benefits of this technology in a variety of noncardiac conditions."

Plasmapheresis has already found a home in the treatment of one cardiac condition: posttransplant cardiomyopathy.

"When there's unexplained left ventricular dysfunction in the absence of cellular rejection or coronary artery disease, we and others have used nonspecific forms of enhancing immunosuppression—among them, plasma exchange—that have led to remarkable results, including sustained and remarkable improvement in ejection fraction. There is significant experience in that setting. It follows logically that this ought to be tested in heart failure, especially if you have the bias that inflammation contributes to the progression of heart failure," Dr. Torre-Amione said.

Building on his own favorable anecdotal experience in two treated patients, Dr. Torre-Amione is doing a formal prospective study of plasmapheresis followed by IVIG in 20 patients with dilated cardiomyopathy and sustained left ventricular dysfunction of more than 6 months' duration. The primary end point will be change in left ventricular ejection fraction at 6 months.

▶ **IVIG.** In one European study involving patients with chronic ischemic or nonischemic cardiomyopathy, IVIG infusions resulted in an increase in ejection fraction from 26% to 31%. The rationale for its use in dilated cardiomyopathy is that IVIG may neutralize harmful circulating antigens and antibodies, block complement, and down-regulate proinflammatory cytokines. It also binds to the Fc receptor on IgI, according to Dr. Baughman.

▶ **Extracorporeal immunoabsorption of cardiac autoantibodies.** The German investigators who pioneered this therapy have presented several studies showing improvement or stabilization of heart function in treated patients with nonischemic dilated cardiomyopathy. In one trial that targeted beta-1 antimyocardial antibodies, 5 days of immunoabsorption resulted in a marked improvement in ejection fraction that was sustained at 12 months.

In another study by the same group, patients with advanced heart failure who had antibodies that fostered reduced calcium movement and depressed myocyte contractility responded to removal of these antibodies through immunoabsorption with an increase in ejection fraction; patients without these antibodies didn't respond.

▶ **Statins.** Statins are known to have anti-inflammatory effects. In 1,186 heart transplant recipients at 12 centers participating in the Heart Transplant Lipid Registry, those on statin therapy had 4% mortality and a 2.4% fatal rejection rate, compared with 13.7% and 7.2%, respectively, in patients not on a statin (Am. J. Cardiol. 2005;95:367-72).

▶ **Celacade immune modulation therapy.** Dr. Torre-Amione was the principal investigator in a favorable phase II clinical trial of a novel proprietary technology to deliver controlled oxidative stress to a small sample of a patient's blood, which is then returned to the patient via intramuscular injection. The oxidative stress results in cell apoptosis, which in turn induces a favorable immune response marked by reduced inflammatory cytokines and increased production of the anti-inflammatory cytokines interleukin-10 and transforming growth factor–β.

In the double-blind, randomized, 6-month trial involving 75 patients with advanced heart failure, there was one death among patients on monthly Celacade therapy, compared with seven in the placebo therapy group. The Celacade group also had significantly fewer hospitalizations.

On the basis of these results, which Dr. Torre-Amione termed "highly provocative," the pivotal ACCLAIM study is under way. ACCLAIM (Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation) is a phase III, 2,000-patient randomized trial headed by James Young, M.D., chairman of the division of medicine at the Cleveland Clinic.

The study sponsor, Vasogen, is also developing Celacade as a therapy for peripheral artery disease. Dr. Torre-Amione is a consultant to the company.

If cumbersome extracorporeal therapies such as immunoabsorption and plasmapheresis prove to have sustained benefit, they may find a role analogous to the role now played by short-term hospitalization for medication adjustment in patients with acute decompensated heart failure.

"It's conceivable that in heart failure patients who have a lot of inflammation, we may reset their syndrome of heart failure by an aggressive anti-inflammatory strategy for a period of time that may have some long-term benefit—maybe not forever, but at least a transient regression in the syndrome," Dr. Torre-Amione said. "Whether or not you can couple this with more chronic immunosuppressive therapy is a more challenging question because of the side effects."

Turning to vasopressin antagonists, Mihai Gheorghiade, M.D., said these agents address two major underserved aspects of heart failure: congestion and hyponatremia. Worsening congestive symptoms—such as dyspnea, edema, and jugular vein distention—are the main reasons for hospital admission in heart failure patients. Yet current therapy targeting congestion is limited to diuretics, which have well-known adverse effects and limited efficacy. Also, roughly 25% of patients hospitalized for heart failure have mild hyponatremia, a strong predictor of poor short-term prognosis.

Three investigational vasopressin antagonists are being developed for patients with both heart failure and hyponatremia. Dr. Gheorghiade is most familiar with tolvaptan, the Otsuka Pharmaceutical Co. drug for which he has conducted clinical trials. Tolvaptan produces a rapid and sustained reduction in body weight due to diuresis without disrupting electrolytes in heart failure patients. This effect is accompanied by normalization of serum sodium within 24 hours in hyponatremic patients, but no significant increase in serum sodium is seen in patients with a normal baseline sodium value. These favorable outcomes are achieved without changes in blood pressure, heart rate, serum potassium, or blood urea nitrogen, unlike with loop diuretics, said Dr. Gheorghiade, professor of cardiology at Northwestern University, Chicago.

The relatively small trials completed to date have shown a trend toward reduced mortality in tolvaptan-treated heart failure patients with hyponatremia, increased BUN levels, or signs of congestion. This suggested benefit is now being definitively evaluated in more than 1,800 patients hospitalized for heart failure in the phase III Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST). The primary end point is 60-day mortality.

"The vasopressin antagonists are going to be an extremely powerful tool, I think, for this population of sick patients with hyponatremia," commented session cochair Michael B. Fowler, M.D., professor of medicine and director of the cardiomyopathy center at Stanford (Calif.) University.

Adrian Iaina, M.D., noted that the prevalence of anemia in patients with heart failure is 40%-50%. Anemia is a powerful risk factor for mortality in heart failure. In 54 published studies, for each 1-g reduction in hemoglobin the risk of mortality increased almost 16%.

Both controlled and uncontrolled small studies show that correction of heart failure anemia with weekly subcutaneous erythropoietin and monthly intravenous iron improves cardiac and renal function and exercise capacity and reduces shortness of breath and fatigue, with a resultant marked decrease in the hospitalization rate. Definitive large randomized trials are ongoing, said Dr. Iaina, head of nephrology at Tel Aviv Sourasky Medical Center. ■

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