Promise of Regenerative Medicine for Rheumatic Diseases

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As regenerative medicine moves into the 21st century, its promise to better treat diseases by using the body's own tissues and systems to repair dysfunction is increasingly becoming a reality. Rheumatologists, like physicians across all specialties, will need to recognize and understand the way in which stem cells function in diseases and how these cells can be harvested and harnessed to provide ever improved treatment options. How are adult stem cells being used in rheumatic diseases? What are some of the key regulatory issues related to the use of embryonic stem cells?

STEM CELLS AND THEIR USE IN RHEUMATIC DISEASES: ADULT STEM CELLS

Alan Tyndall, MD, University of Basel, Basel, Switzerland, presented current data on the application of adult or postnatal stem cells in autoimmune diseases. He focused the talk on the hematopoietic stem cell transplantation (HSCT) program that has been underway for about the past 15 years, as well as the newer, still evolving program in mesenchymal stromal cell transplantation.

HEMATOPOIETIC STEM CELL TRANSPLANTATION PROGRAM

Since September 2011, about 1500 patients in Europe have received HSCT as listed on the European Group for Blood and Marrow Transplantation Registry. Most of these patients have undergone transplantation for multiple sclerosis (n=476) followed by connective tissue disease (n=427). In the United States, ~500 patients with severe autoimmune diseases have received transplantation. The concept of HSCT transplantation for autoimmune disease is to replace ablated immune and hematopoietic systems to allow deep immunosuppression that may then permit resetting autoimmunity.

Currently, four prospective randomized clinical trials have been performed to evaluate the efficacy of HSCT for autoimmune diseases. Three of these trials evaluate the efficacy of HSCT for patients with systemic sclerosis (scleroderma), and one trial for Crohn's disease (Table 1).

For example, the ASTIS trial [ISRCTN54371254] is a multicenter, multinational, investigator-initiated, prospective trial that has enrolled 156 patients with poor prognosis early diffuse cutaneous systemic sclerosis [van Laar JM et al. EULAR 2012 (abstr LB0002)]. Patients were randomized to HSCT (n=79) or control (n=77). As of May 2012, the study has shown that patients treated with HSCT had significantly better long-term, event-free, and overall survival despite ~10% treatment-related mortality compared with controls (who received 12 months of intravenous cyclophosphamide). The study also found smoking status as a determinant of event-free and overall survival after HSCT, with a reduction in event-free and overall survival in smokers. Secondary outcomes of the study also showed that HSCT patients felt better overall than controls based on measures such as mRSS as well as other clinical outcomes.

Table 1. Clinical Trials to Evaluate Efficacy of HSCT for Autoimmune Diseases

Trial	Primary Endpoint	Status
ASTIS (scleroderma; n=156) European Study [ISRCTN54371254]	Event-free survival (ie, event as organ failure or death)	Last patient randomized October 2009 Superior event-free survival from 2 years onward in transplant arm Treatment-related mortality of 10%
SCOT (scleroderma; n=75) United States study [NCT00114530]	Composite endpoint (death, end organ failure) at 54 months	Recruitment ended in May 2011
ASSIST (scleroderma; n=19) United States (Chicago) single-center study	Modified Rodnan skin score and or lung function at 12 months	Published [Burt K et al. *Lancet* 2011] Achieved endpoint; two relapses
ASTIC (Crohn's disease; n=45) European Study [NCT00297193]	Proportion of patients in sustained remission at 1 year	34 patients out to 12 months; early treatment efficacy One treatment-related death in early treatment arm

Overall, Dr. Tyndall emphasized that what has been learned over the past 15 years is that it is possible to reset autoimmunity in some patients, and that the responses are durable, including in some cases loss of autoantibodies, and not just due to long-term immunosuppression. He also emphasized that there will always be some treatment-related-mortality and toxicity, which, he said may be possible to reduce by better patient selection (eg, selecting patients who do not smoke). Finally, he emphasized the need to transplant before irreversible organ damage occurs.

MESENCHYMAL STROMAL CELL TRANSPLANTATION

A newer, still evolving type of stem cell transplantation is the use of mesenchymal stromal cells for transplantation for severe autoimmune diseases. The promise of the use of these cells for transplantation is based on the concept that mesenchymal stromal cells home to inflamed tissue, provide

an anti-inflammatory effect, and may be able to repair damaged tissue. A number of Phase 1 and 2 uncontrolled clinical trials are underway using these cells in autoimmune disease, and current data suggest that acute toxicity appears low. However, long-term safety is not known and the current evidence suggests the need for tumour surveillance as well as adequately powered controlled studies.

REGULATION OF EMBRYONIC (PLURIPOTENT) STEM CELLS

Unlike adult stem cells, investigation into the use of pluripotent stem cells for rheumatic diseases as well as other diseases is very young with only three ongoing trials of these cells currently under way in the United States. According to Melissa Carpenter, PhD, Carpenter Group Consulting, Seattle, Washington, USA, key issues regarding these cells and their potential therapeutic use revolve around regulation of stem cell products due to their fundamental characteristic of living cells. She highlighted the unique challenge of developing cell products from these cells and preclinical testing of these products. Among the challenges of developing pluripotent stem cell products are safety concerns due to the cell's unlimited proliferative capacity (which raises concerns about their stability over the long term) as well as their pluripotency (which raises concerns about teratoma formation).

Challenges to preclinical testing of pluripotent stem cell products include the lack of a standard set of preclinical tests and testing parameters applicable to all products, and the need for a case-by-case strategy for preclinical regulatory testing based on the diversity and biological properties of products derived from these cells. Table 2 highlights key issues that regulatory agencies need addressed prior to approving preclinical study designs.

Table 2. Issues for Approving Preclinical Study Designs

What is the optimal animal model?
What is the efficacious dose, and maximum feasible dose?
What is the optimal delivery site? Optimal method? Optimal timing?
Where do the cells go?
How long do the cells persist?
How do the cells change?
What happens to the host tissue?

Various kinds of preclinical study designs include studies to assess the pharmacology and proof-of-concept of pluripotent stem cell products in relevant animal models of disease, studies to assess safety and toxicity in healthy animals, and studies with a hybrid pharmacology-toxicology study design.

Overall, Dr. Carpenter said that despite the many hurdles to develop pluripotent stem cell products and get them approved for preclinical testing, the field is moving very quickly.