Bone marrow-derived stem cells may offer novel therapeutic option for skin disorder

December 4 2008

Stem cells derived from bone marrow may serve as a novel therapeutic option to treat a disease called epidermolysis bullosa (EB), a disorder characterized by extraordinarily fragile skin, according to a study prepublished online in *Blood*, the official journal of the American Society of Hematology.

Epidermolysis bullosa is a disorder characterized by extraordinarily fragile skin and blistering on touch, akin to third degree burns. While the disease is often lethal in the neonatal period, more severe forms of the disease, such as recessive dystrophic EB (referred to as RDEB), can lead to years of painful blistering and mutilating scarring. The condition is caused by significantly reduced collagen type 7 protein (col7) production, a key component of the anchoring fibrils that connect the cutaneous membranes to the dermis of the skin and mucosal tissues in the gastrointestinal tract. A lack of these fibrils means the dermal-epidermal connection is very sensitive, and any action, which can include simple functions such as walking or eating, and the touch of clothing, creates friction between the skin layers that creates blisters and painful sores.

Children with RDEB, who are often referred to as “butterfly children” because their skin is said to be as sensitive as butterfly wings, develop painful skin and mucosal blistering, mutilating scarring, alopecia (hair loss), and other erosions shortly after birth. As a result of the extreme fragility of the skin and the chronic trauma of friction, RDEB patients often develop squamous cell carcinomas (a form of skin cancer). There

is currently no cure for the disease, and palliative care includes complex bandaging, surgical removal of damaged tissue, and nutritional support.

“We have been looking into stem cells as viable treatment options for correction of conditions such as epidermolysis bullosa, because they can produce extracellular matrix proteins,” said Jakub Tolar, MD, PhD, of the University of Minnesota and lead author of the study. “In this condition, the skin, the largest organ in the body, can significantly benefit from a renewable source of healthy cells that can help improve the connection between the dermis and epidermis and strengthen the skin against everyday stresses.”

In this study, researchers worked with a mouse model of RDEB-infused bone marrow cells to determine if they would increase production of the col7 protein and formation of anchoring fibrils, and improve survival in the mouse recipients. The research team used bone marrow cells enriched for hematopoietic (stem cells that can develop into most blood cell types) and progenitor cells to increase the concentration of cells with the capacity to produce col7. The team tested these cells against non-enriched stem cells to determine their benefit to the treated mice.

Results of the study found that when injected into mice with RDEB, these specially selected marrow-derived stem cells diminished the disease process. They traveled to the diseased skin areas, increased protein and anchoring fibrils, prevented blister formation and extended survival. In contrast to other marrow cells, the selected cells extended the median survival time versus untreated or non-enriched marrow-treated recipients (10.0 versus 5.6 versus 6.0 days, respectively). Three of the 20 mice treated with the enriched cells benefited enough from the treatment to survive longer than the treatment period (untreated RDEB mice usually die within two weeks). Importantly, each survivor demonstrated marked improvement of new blister formation (blisters develop consistently in the areas of trauma, including footpads due to walking or

in the oral cavity due to eating) with some evidence of old blisters healing.

“Our data provide the first evidence that a selected population of marrow cells can connect the epidermis and dermis in a mouse model of the disease and offer a potentially valuable approach for treatment of human RDEB and other extracellular matrix disorders. These results provide proof of principle of bone marrow transfer to repair the basement membrane defect in RDEB, and they warrant a clinical trial to assess the safety and efficacy of treatment of human RDEB by means of hematopoietic cell transplantation,” said Dr. Tolar.

Research suggests that the systemic infusion of wild-type bone marrow cells could provide benefit to other human disorders of the extracellular matrix. Efforts are underway to identify the requirements of bone marrow-derived stem cells capable of efficiently homing to wounded skin and producing an array of extracellular matrix proteins. As the principal advantage of systemic therapy is its potential to target not only the skin but also the mucosa of the mouth and gastrointestinal tract, the clinical testing of efficacy of human bone marrow for the treatment of human RDEB is underway to determine whether it is of more substantial benefit than local protein, gene, or cellular therapies currently being investigated by other researchers.

An estimated 50 in 1 million live births are diagnosed with EB. The disorder occurs in every racial and ethnic group throughout the world and affects both sexes.

Source: American Society of Hematology