Infants with rare bone disease improve bone formation after cell transplantation

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Recent research carried out by a team of researchers in Japan has investigated the use of bone marrow transplants (BMTs) to treat hypophosphatasia (HPP). In this study, the researchers carried out BMT for two infants with HPP in combination with allogenic (other-donated) mesenchymal stem cell transplants (MSCTs). The allogenic MSC donors were a parent of the infant.

The study will be published in a future issue of *Cell Transplantation* and is currently freely available on-line as an unedited early e-pub.

"Hypophosphatasia" (HPP) is a rare and most often fatal genetic bone disease affecting infants that has no current treatment. The disease is caused by mutations in the ALPL gene, which encodes alkaline phosphatase (ALP). Patients with severe HPP develop bone impairment and have extremely low levels of ALP activity, an enzyme necessary for bone mineralization.

Although there are mild and more severe forms, severe hypophosphatasia prevents proper bone mineralization during perinatal development. When the disease develops perinatally, many infants are still-born, with little evidence of bone mineralization. HPP can also appear in later infancy, generally before an infant reaches the age of six months, with the result that most afflicted infants do not live past the age of six months. Milder forms of HPP can present in later youth or in adulthood.

"Mesenchymal stem cells (MSCs) reside in bone marrow and other tissues and have a self-renewal capacity so that after transplantation they can differentiate into various cell lineages, including bone and cartilage," said Dr. Takeshi Taketani of the Division of Blood Transfusion at Shimane University Hospital in Shimane, Japan. "We performed multiple infusions of MSCs for two infant patients with severe HPP who had already undergone BMT. The adverse events from the BMT were managed and there were no adverse events from the MSC infusions."

After each infant had undergone BMT, one infant received four MSCTs and a second infant received nine MSCTs. Previous research had revealed that MSCT without a prior BMT was ineffective.

The researchers reported that the two infants receiving both BMT and MSCTs improved not only in terms of bone mineralization, but also saw improvements in muscle mass, respiratory function and mental development. Both children continue to survive at age three.

"Our data suggest that allogenic MSCT combined with BMT might be one of the safer and more effective remedies for patients with severe HPP, although long-term effectiveness remains unknown and warrants further study," concluded the researchers. "We need to establish curative, MSC-based treatment strategies that can maintain the long-term survival and differentiation capabilities of transplanted allo-MSCs."

"This study highlights the promise of stem cells in presenting a new frontier for regenerative medicine, with an improvement of HPP-associated symptoms and survival following BMT and MSCT." said Dr. David Eve, *Cell Transplantation* associate editor, and Instructor of neurosurgery and brain repair at the University of South Florida School of Medicine. "In order to elucidate the mechanisms behind recovery and further extrapolate the study to all HPP patients, a larger cohort and more long term follow-up are needed."

More information: Taketani, T.; Oyama, C.; Mihara, A.; Tanabe, Y.; Abe, M.; Hirade, T.; Yamamoto, S.; Hattori, M.; Katsube, Y.; Ohnishi, H.; Sasao, M.; Oda, Y.; Hattori, K.; Yuba, S.; Ohgushi, H.; Yamaguchi, S. Ex Vivo Expanded Allogeneic Mesenchymal Stem Cells with Bone Marrow Transplantation Improved Osteogenesis in Infants with Severe Hypophosphatasia, *Cell Transplant*. Appeared or available on-line: November, 13, 2014

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