

NON-TECHNICAL ABSTRACT

The outlook for children with severe osteogenesis imperfecta (OI) is poor. The only therapeutic option intended to ameliorate their symptoms is treatment with one of the bisphosphonate drugs. The issues are that it is life-long therapy, the long-term adverse effects are not known and animal models suggest they could be significant, and it does not address the underlying pathology. It is unlikely that drug therapy will ever cure this disorder. Our previous studies of allogeneic bone marrow transplantation (BMT) and allogeneic marrow stromal cell infusion post BMT suggest that marrow-derived mesenchymal cells go to the bone, become bone cells and stimulate growth, bone mineralization and a reduction of fractures.

Our results thus far suggest this approach of cell therapy holds great promise; however, there are several outstanding issues. The growth and mineralization must be greater both in magnitude and duration than is currently observed for this therapy to be broadly applied to children with severe OI. Second, we must have a better understanding of the marrow cells that give rise to the bone and presumably account for the clinical benefits observed in these children.

This protocol is designed to address the issues outlined above. The primary purpose of this protocol is to determine the safety and feasibility of BMT with a bone marrow to which marrow mesenchymal (stromal) cells have been added. The hypothesis is that transplanting more bone making cells will result in greater engraftment and an improved clinical outcome. We will also genetically mark the stromal cells as well as some CD34 cells, which are thought to be the cells that give rise to blood. By using two distinguishable markers, we will be able to discern the two cell populations and determine the bone making potential of each. This issue can only be resolved by using a gene marking strategy. Thus, these studies will not only begin to explore the clinical potential of adding cells to the bone marrow in the context of BMT, but will also serve as the foundation for future studies of cell therapy, and possibly gene therapy, of genetic disorders of bone.