Cell-based immunotherapy with mesenchymal stem cells cures bisphosphonate-related osteonecrosis of the jaw-like disease in mice.

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Authors: Takashi Kikuiri, Insoo Kim, Takyoshi Yamaza, Kentaro Akiyama, Qunzhou Zhang, Yunsheng Li, Chider Chen, WanJun Chen, Songlin Wang, Anh D Le, Songtao Shi
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Public Summary:
In this work, we developed a murine model of bisphosphonate-related osteonecrosis of the jaw (BRONJ), a morbid bone disease associated with long-term bisphosphonate use. Bisphosphonates belong to a new class of anti-bone resorptive drug widely used for almost 30 years in patients with a variety of skeletal related complications, such as osteoporosis, Paget’s disease, and tumor metastasis to bone. The majority of BRONJ cases (94%) have been reported in patients receiving high doses of intravenous aminobisphosphonates (primarily zoledronic acid and pamidronate) for oncologic conditions. The estimated incidence of BRONJ in patients receiving intravenous bisphosphonates for malignant disease ranges from 0.8% to 12%. Patients with BRONJ present various jaw symptoms, including pain, swelling, infection, loose teeth, and exposed bones in some severe cases. Most attempts to control this disorder have not been successful; conservative non-surgical approaches have been recommended in managing BRONJ patients which only slows down the deterioration but does not cure the disease. To develop effective approach to prevent and treat BRONJ becomes an urgent issue for patients using bisphosphonates. Despite convincing evidence of an association between bisphosphonates usage and BRONJ, up to date there is no scientific evidence supporting a direct causal effect. Furthermore, due to the lack of a testable animal model in mice and large animals, and limited biological tissue specimens in clinics, the patho-physiological mechanisms underlying BRONJ remain largely unknown. In this study, we developed a mouse model of BRONJ that recapitulates major clinical and radiographic manifestations of the human disease, including its characteristic features of delayed healing displayed orally as an open alveolar socket without mucosal coverage, exposed necrotic bone or sequestra, increased inflammatory infiltrates, osseous sclerosis, and radio-opaque alveolar bone in the jaw. Using our established murine model, we demonstrated for the first time a direct link between high dose of zolendronate and human BRONJ-like disease. Mechanistically, zolendronate induced BRONJ-like phenotype in part by suppressing the adaptive regulatory T cells, Tregs, and increasing the inflammatory interleukin 17 (IL17) producing T helper cells, Th17, in peripheral blood. The alteration in the balance between Tregs and Th17 was observed in zolendronate/dexamethasone-treated mice, not in dexamethasone or non-treated control mice, and is restored in mice undergo salvage therapy to replenish Tregs or Pan-T cells. More importantly, cell-based therapy using systemic mesenchymal stem cell (MSC) infusion can prevent or cure BRONJ via re-establishment of the immune balance between Treg and Th17, similar to Treg replenishing treatment. Our findings provide “proof-of-concept” that patho-physiological mechanism of BRONJ is associated with altered immunological homeostasis and targeting the immune function using Treg replenishing infusion and mesenchymal stem cell therapy may open a new avenue for preventive and therapeutic intervention of human BRONJ diseases.

Scientific Abstract:
Patients on high-dose bisphosphonate and immunosuppressive therapy have an increased risk of bisphosphonate-related osteonecrosis of the jaw (BRONJ); despite the disease severity, its pathophysiology remains unknown, and appropriate therapy is not established. Here we have developed a mouse model of BRONJ-like disease that recapitulates major clinical and radiographic manifestations of the human disease, including characteristic features of an open alveolar socket, exposed necrotic bone or sequestra, increased inflammatory infiltrates, osseous sclerosis, and radiopaque alveolar bone. We show that administration of zolendronate, a potent aminobisphosphonate, and dexamethasone, an immunosuppressant drug, causes BRONJ-like disease in mice in part by suppressing the adaptive regulatory T cells, Tregs, and activating the inflammatory T-helper-producing interleukin 17 cells, Th17. Most interestingly, we demonstrate that systemic infusion with mesenchymal stem cells (MSCs) prevents and cures BRONJ-like disease possibly via induction of peripheral tolerance, shown as an inhibition of Th17 and increase in Treg cells. The suppressed Tregs/Th17 ratio in zolendronate- and dexamethasone-treated mice is restored in mice undergoing salvage therapy with Tregs. These findings
provide evidence of an immunity-based mechanism of BRONJ-like disease and support the rationale for in vivo immunomodulatory therapy using Tregs or MSCs to treat BRONJ.

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