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Study pinpoints genetic variation that raises a risk linked to bisphosphonates

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Researchers at the Columbia University College of Dental Medicine have identified a genetic variation that raises the risk of developing serious necrotic jaw bone lesions in patients who take bisphosphonates, a common class of osteoclastic inhibitors. The discovery paves the way for a genetic screening test to determine who can safely take these drugs. The study appears in the online version of the journal *The Oncologist*.

Oral bisphosphonates are currently taken by some 3 million women in the United States for the prevention or treatment of osteoporosis. In addition, intravenous bisphosphonates are given to thousands of cancer patients each year to control the spread of bone cancer and prevent excess calcium (hypercalcemia) from accumulating in the blood. Bisphosphonates work by binding to calcium in the bone and inhibiting osteoclasts, bone cells that break down the bone's mineral structure.

"These drugs have been widely used for years and are generally considered safe and effective," said study leader Athanasios I. Zavras, DMD, MS, DMSc, associate professor of Dentistry and Epidemiology and Director of the Division of Oral Epidemiology & Biostatistics at the Columbia University College of Dental Medicine. "But the popular literature and blogs are filled with stories of patients on prolonged bisphosphonate therapy who were trying to control osteoporosis or hypercalcemia only to develop osteonecrosis of the jaw."

Osteonecrosis of the jaw, or ONJ, often leads to painful and hard-to-treat bone lesions, which can eventually lead to loss of the entire jaw.

Among people taking bisphosphonates, ONJ tends to occur in those with dental disease or those who undergo invasive dental procedures.

There are no reliable figures on the incidence of ONJ in patients taking oral bisphosphonates. Estimates range from 1 in 1,000 to 1 in 100,000 patients for each year of exposure to the medication, according to the American College of Rheumatology. ONJ is more common among cancer patients taking the intravenous form of the drug, affecting about 5 to 10 percent of these individuals, noted Dr. Zavras.

Studies have suggested that genetic factors play a major role in predisposing patients to ONJ. Delving deeper into this question, Dr. Zavras and his colleagues performed genome-wide analyses of 30 patients who were taking bisphosphonates and had developed ONJ and compared them with several bisphosphonate users who were disease free.

The researchers found that patients who had a small variation in the RBMS3 gene were 5.8 times more likely to develop ONJ than those without the variation. The study also identified small variations in two other genes, IGFBP7 and ABCC4, that may contribute to ONJ risk.

"Our ultimate goal is to develop a pharmacogenetic test that personalizes risk assessment for ONJ, a test that you could give to people before they start to use bisphosphonates," said Dr. Zavras. "Those who are positive for this genetic variation would select some other treatment, while those who are negative could take these medications with little fear of developing ONJ."

"At the moment, many women discontinue or avoid treatment for serious osteoporosis because they are afraid of losing their jaw bones," added Dr. Zavras. "There even are reports of dentists who have refused to perform certain invasive procedures in patients taking

bisphosphonates. So there is a great need for a pharmacogenetic screening test to determine which patients are really at risk for ONJ."

The current study looked only at Caucasians. Further studies are needed to determine whether the RBMS3 gene variation is seen in other racial groups, according to the researchers.

The paper is entitled, "Genome-wide pharmacogenetics of bisphosphonate-induced osteonecrosis of the jaw: the role of RBMS3." The lead authors are Paola Nicoletti of CUMC and Vassiliki M. Cartsos of Tufts School of Dental Medicine. The other contributors are Penelope K. Palaska of Tufts and Yufeng Shen and Aris Floratos at the Columbia University Medical Center Bioinformatics Department.

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Columbia University has filed a patent application with the United States Patent and Trademark Office relating to a genetic screening test for predisposition to ONJ, and, through its technology transfer office, Columbia Technology Ventures, is actively seeking partners to collaborate, license and commercialize the technology.

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