

Gene therapy demonstrates benefit in patients with rheumatoid arthritis

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Researchers have reported the first clinical evidence that gene therapy reduces symptoms in patients with rheumatoid arthritis, an important milestone for this promising treatment which has endured a sometimes turbulent past. Described in the February issue of the journal *Human Gene Therapy* the findings stem from a study of two patients with severe rheumatoid arthritis conducted in Germany and led by an investigator at Beth Israel Deaconess Medical Center (BIDMC).

Originally conceived as a means of treating genetic diseases, such as cystic fibrosis and hemophilia, gene therapy involves implanting a normal gene to compensate for a defective gene in the patient. The first clinical trial to test gene therapy was launched in 1990 for the treatment of a rare, genetic immunodeficiency disease.

"This study helps extend gene therapy research to nongenetic, nonlethal diseases," explains principal investigator Christopher Evans, PhD, Director of the Center for Advanced Orthopaedic Studies at BIDMC. "Rheumatoid arthritis [RA] is an extremely painful condition affecting multiple joints throughout the body. Arthritis is a good target for this treatment because the joint is a closed space into which we can inject genes," adds Evans, who is also the Maurice Muller Professor of Orthopaedic Surgery at Harvard Medical School.

A classic autoimmune disease, RA develops when, for unknown reasons, the body's immune system turns against itself, causing joints to become swollen and inflamed. If the disease is inadequately controlled, the

tissues of the joint are eventually destroyed. Although anti-inflammatory agents and biologics can help to mitigate symptoms, there is no cure for the condition, estimated to affect more than 2 million individuals in the U.S. alone.

Evans has spent many years studying the molecules responsible for the breakdown of cartilage in patients with arthritis, identifying interleukin-1 as a good target. But, he adds, once he had this answer, another question was not far behind: How could he effectively reach the joints to block the actions of this protein?

Gene therapy provided the answer.

By implanting a gene in the affected joint, he was able to stimulate production of a human interleukin-1 receptor antagonist protein, which serves to block actions of the interleukin-1 protein.

"The idea is that by remaining in place, the new gene can continuously block the action of the interleukin-1 within the joints," says Evans. "In essence, the gene becomes its own little factory, continuously working to alleviate pain and swelling."

In 2005, in a study published in the *Proceedings of the National Academy of Sciences (PNAS)*, Evans and colleagues demonstrated that the IL-1Ra gene could be safely transferred to human joints in patients with RA. In this new paper, the authors aimed to prove that the therapy was not only safe, but that it was of therapeutic benefit.

Two study subjects were recruited. (The number reduced from six study subjects following severe adverse events in an unrelated gene therapy trial taking place elsewhere, according to Evans.) Both subjects were postmenopausal females under the age of 75 with a diagnosis of advanced rheumatoid arthritis. After tissue was removed from the

subjects' knuckle joints, a harmless retrovirus was inserted into the tissue cells, in order to serve as a "vector" to transport the gene into the patients' joints. After being placed in culture to grow and replicate, the cells were injected back into the afflicted joints.

After four weeks, patients reported reduced pain and swelling, according to Evans. "In one of the two subjects, these effects were dramatic, and the gene-treated joints remained pain-free even though other joints experience flares." Subsequent laboratory tests showed that tissues removed from the subject's joint tissue synthesized lower amounts of disease-related proteins, confirming that the reduction in pain and swelling resulted from the actions of the implanted gene.

"Existing treatments for rheumatoid arthritis are costly and need to be administered regularly," says Evans, adding that in addition to risk of side effects, not all patients respond well. "This paper provides us with the first real evidence that painful symptoms can indeed be lessened through gene therapy."

Ongoing work will focus on the use of gene therapy for the treatment of osteoarthritis, as well as rheumatoid arthritis.

Source: Beth Israel Deaconess Medical Center

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