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GENE THERAPY IN ORTHOPEDICS

An essay

Submitted for partial fulfillment of master degree in orthopaedics

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Introduction

Introduction

Gene therapy may be defined as the introduction of a form of nucleic acid into the cells of a patient for the amelioration of a disease process. There are three basic approaches to the this lofty goal of disease amelioration: (1) replacement of defective genes; (2) augmentation of normal gene function (or interference with proliferative controls); and (3) blocking of disease triggering genes (oncogenes) at the RNA or DNA levels.(1)

Human gene therapy currently is limited to manipulations affecting somatic, differentiated cells. The risk of inadvertent transfer into reproductive cells is low and difficult to quantitate. Such concerns can be minimized and should not act as an absolute contraindication for proceeding with Phase I trials for diseases that cause serious disability. Germ line gene therapy where reproductive cells are being manipulated is unlikely to become accepted in the foreseeable future. This is because the potential risk and unpredictable results may be transferred to the patient's descendents. Specific legal restrictions have been developed in Europe to prevent attempts at germ line therapy. (2)

Somatic cell therapy can be seen as a special form of organ transplantation with a specific transfer of information without surgical intervention. Somatic gene therapy has a limited duration of effect and will have to be repeated on a regular basis because the somatic cells of the body constantly are being replaced. Four thousand monogenetic deficiencies are candidates for somatic gene therapy. Additionally targeted elimination of cancer cells, treatment of AIDS, vascular disorders, rheumatoid disorders and cell marking have been the basis of clinical trials using gene therapy.(2)

In the late 1960s, initial thoughts were entertained on the introduction of genes into somatic cells to treat genetic defects. It was not until the necessary technologic advancements evolved that such ideas received widespread enthusiasm. As of June 1999, there were 313 approved clinical trials that use gene therapy with more than 2000 patients enrolled. Initial efforts were focused on monogenetic disorders but because of the limited number of patients afflicted subsequent studies have focused on AIDS and cancer. The latter two indications now constitute approximately 80% of the current approved trials. Goals of nearly all of these studies are to establish safety rather than efficacy. The majority of the studies are in preclinical assessment or in Phase I trials. There are a limited number of Phase II trials ongoing and only one Phase III trial that is an international multicenter trial focusing on glioblastoma. (3)

Until recently, the risk associated with the ongoing trials had been minimized. The theoretical concerns of adenoviral vectors include vector induced inflammation via immune activation and complementation of the modified virus with wild type viruses leading to overwhelming infection. One patient in an early trial of cystic fibrosis experienced acute adverse effects after bronchoscopic placement of an adenoviral vector. The patient's symptoms included fever, dyspnea, hypotension, and pulmonary consolidation, which resolved spontaneously over 2 weeks. In September 1999, the first fatality occurred as part of a trial that focused on orthnithine transcarbamylase using an adenovirus infusion into the liver. One of the 18 patients treated went into multisystem organ failure and died 4 days after treatment. The presumed cause of death is an immune response to the viral protein. Because the majority of trials use incompetent adenovirus as a vector, it raises the question as to whether