Gene therapy

Applications

By Nicola Stoner, PhD, MRPharmS

Gene therapy is an emerging area of medicine, with most gene therapy products currently at the experimental stages of development. The world’s first gene therapy product was licensed in China in 2004 and the first in Europe is expected to be licensed in the next few years. Both of these treatments are for cancer.

Pharmacists need to be prepared to deal with this new group of medicines. They will need to help NHS organisations adhere to legislation and guidelines relating to genetically modified organisms and ensure that facilities are appropriate, staff are adequately trained and standard operating procedures are in place. A White Paper on genetics, updated by the Department of Health in 2008, highlights gene therapy as a priority for NHS research. As research into genetics, recombinant DNA technologies and individual diseases progresses, the number of gene therapies is bound to increase.

Diseases potentially treated by gene therapy

The absence of certain cellular or biological factors, for example enzymes, in some diseases can be due to a gene being defective. Gene therapy can deliver to target cells genes that code for the missing biological factor. Cancer, infectious diseases, cardiac disease, neurological disorders and some inherited conditions are among the areas into which gene therapy research is being carried out.

Cancer

Gene therapy strategies against cancer include the introduction of tumour suppressor genes, genes that induce apoptosis, genes that inhibit tumour angiogenesis and genes coding for an enzyme to convert prodrugs to active drugs, and immunotherapy. Cancers for which gene therapy products are being developed include glioblastoma, metastatic melanoma, head and neck cancer, non-small cell lung cancer, prostate cancer, renal cell cancer and colorectal cancer.

SUMMARY

Gene therapy has the potential to treat a variety of cancers, neurological disorders and infectious diseases, as well as cardiac diseases and several inherited conditions.

Many clinical trials are currently investigating the effectiveness of gene therapies so, although there are currently no such treatments licensed in Europe, this branch of medicine is likely to expand in the future.

Some cancers, such as malignant melanoma, are particularly sensitive to immunotherapy, and gene therapy vaccines are being developed against such cancers. Other cancers have specific tumour antigens that can be targeted with gene therapy, for example carcinoembryonic antigen in colorectal cancer or 5T4, which is found on most solid tumours (see below). Some gene therapies have been developed to target defective genes in cancer patients, for example the p53 gene (see “Pipeline”, p272).

TroVax, an experimental gene therapy, targets the tumour antigen 5T4 and is delivered by the “modified vaccinia Ankara” (MVA) vector (see accompanying article discussing vector technologies, p261). Tumour antigen 5T4 is a surface glycoprotein expressed on 80–90% of solid tumours but with low expression in normal tissue. 5T4 expression occurs throughout the whole tumour and correlates with poor prognosis. TroVax has been tested in phase I and phase II clinical trials in colorectal, renal and prostate cancer patients. Results showed antibody or cellular responses, or both, against 5T4 in most of the patients who were treated, which correlated with clinical benefit. Two or three vaccinations were required to induce the 5T4-specific antibody responses. Randomised, placebo-controlled phase III trials need to be undertaken to assess further the place of this treatment in practice.

Neurological disorders

Neurological disorders that could be treated with gene therapy include Parkinson’s disease, Alzheimer’s disease and motor neurone disease.

As an example, ProSavin is currently being trialed for Parkinson’s disease, which is caused by dopamine deficiency in the brain. ProSavin delivers into the brain, via a lentivirus vector, genes that encode for three enzymes required for dopamine synthesis.
The aim is for target cells to begin dopamine production and restore levels of the neurotransmitter in the brain. ProSavin has been tested in phase I and II clinical trials, in which clinical efficacy has been reported. No adverse drug reactions were observed, patients had an improved quality of life and the medicine was shown to be safe for up to 12 months. Further clinical trials are currently in progress to evaluate higher doses of ProSavin.

Infectious diseases Gene therapy vaccines are being developed and trialed for tackling infectious diseases, including tuberculosis, malaria, HIV and influenza. Tuberculosis vaccines are being studied that use genetically modified vaccinia comprising a recombinant fowl pox virus and a recombinant MVA virus, each containing a tuberculosis antigen. Malaria vaccines undergoing trials utilise chimpanzee adenovirus containing a malaria antigen.

A randomised, double-blind, placebo-controlled phase II study of gene therapy has been undertaken in 74 patients with HIV-1 infection. The patients received either an anti-HIV ribozyme (OZ1) or placebo. Cells from individual patients were removed and treated with the gene therapy before being infused back into the patient (ie, ex vivo gene therapy with autologous haematopoietic progenitor cells). Results showed the viral load was reduced in patients receiving OZ1, compared with placebo, 100 weeks after treatment. CD4+ lymphocyte counts were higher in the OZ1 group throughout the 100 weeks. Such therapeutic vaccines have the potential to preserve the immune system and reduce the need for lifelong treatment with antiretrovirals for people with HIV.

Inherited diseases For people with inherited diseases, gene therapy could replace a defective or missing gene or express a missing biological factor, enzyme or protein.

Haemophilia For people with haemophilia, therapies could be designed to deliver genes that express the missing factors VIII and IX, meaning individuals would no longer need to inject exogenous clotting factors. Research is being undertaken with adeno-associated virus and lentivirus vectors.

Cystic fibrosis Cystic fibrosis is caused by mutations in the gene that encodes a cellular protein called “cystic fibrosis transmembrane conductance regulator” (CFTR). This mutation results in abnormal ion transportation within lung and other cells. The CFTR gene has been cloned and researchers are now developing gene therapies to enable expression of CFTR. Non-viral vectors are undergoing trials to deliver gene therapy locally to the lungs via nebuliser.

Inherited retinal degeneration Ocular gene therapies could offer a treatment strategy for people with inherited retinal degeneration. Both viral and non-viral vectors are being researched. The genetic and biological backgrounds of ocular diseases are well defined and so gene therapy can be targeted appropriately.

For example, in Leber congenital amaurosis type 2, a type of hereditary blindness, photoreceptor cells are unable to respond to light because of a defect in the RPE65 gene. An adeno-associated virus was used in a phase I clinical trial to deliver a functioning RPE65 gene to the retina. The study showed an acceptable side-effect profile for the product and patients said that their vision had improved slightly.

Severe combined immunodeficiencies “Severe combined immunodeficiencies” (SCID) is an inherited disorder that leaves affected children without fully functional immune systems. This can lead to severe recurrent opportunistic infections, which can be fatal. The most common types of SCID are SCID-ADA (which is due to adenosine deaminase deficiency) and SCID-XI (X-linked SCID, due to a defect on the X-chromosome). The most successful treatment is a bone marrow transplant from a related or compatible donor. However, finding a suitable donor can be difficult and graft-versus-host disease is a common complication. SCID-ADA can be treated with enzyme replacement therapy of the ADA enzyme, which is administered weekly; however, this can cause side effects.

Gene therapy was studied in humans for the first time in 1990 — for children with SCID-ADA. Trials have explored the use of, for example, retroviral vectors to deliver the ADA gene to patients with SCID-ADA. There are reports of patients still being alive two to eight years after receiving gene therapy for SCID in clinical trials.

Cardiac disease Gene therapy has been investigated to target angiogenesis (the formation of new blood vessels)
suitable risk assessments have been carried out. training and awareness are adequate and documented. standard procedures have been implemented and are followed.

Clinical focus

there are currently no gene therapies licensed for use in europe. an application for the gene therapy cerepro (sitimogene ceradenovec) is being assessed by the european medicines agency (emea); the indication under scrutiny is for operable malignant glioma, a type of brain cancer. if approved, cerepro could become europe’s first gene therapy treatment for cancer. cerepro comprises an adenoviral vector, administered by injection into the brain after surgical removal of the tumour. this gene therapy induces the healthy brain cells to express an enzyme, thymidine kinase, which converts ganciclovir (given intravenously to the patient) to a product that kills dividing cells — thus preventing the growth of further tumour cells. since healthy neurons are non-dividing they are not affected by this treatment.2

In 2008, applications for advexin (a p53 gene therapy) were submitted to the US food and drug administration and the emea.13 This treatment — the first of a new class of tumour suppressor cancer therapy — would be indicated for recurrent, refractory head and neck cancer. advexin works by using the body’s natural tumour suppressor mechanisms to kill the cancer. tumour suppressor genes, such as p53, normally restrain cell growth, but if they are missing or inactivated by a mutation cells can grow uncontrolled. P53 abnormalities are found in most solid tumours. advexin delivers the normal tumour suppressor p53 gene to target cells, aiming to replace p53 function without harming normal cells. patients would require diagnostic tests to analyse the p53 status of their tumour to ensure their suitability for this treatment.14

side effects

A serious potential side effect of gene therapy is the triggering of a patient’s immune system to attack the vectors carrying therapeutic genes. in 1999, an 18-year-old man died as a result of a massive cytokine storm triggered by an adenovirus vector given in a clinical trial for ornithine transcarbamylase deficiency.12

other side effects can be caused by therapeutic genes being inserted at an inappropriate place in the genome causing, eg, cancer or other mutations (see p264 of accompanying article).11,12 Side effects can also be caused by over-expression of the gene product.

monitoring

There is also a risk of transmission of viral vectors from the patient to other individuals or the environment. Patients are monitored to assess whether they shed viral vectors after in vivo administration, or to assess the cellular migration of the vector after ex vivo administration. swabs are taken from areas where gene therapy has been administered, and also from the patient, and tested for the presence of the product using a specific DNA assay.

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pipeline

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handling

Products containing genetically modified organisms are divided into four classes depending on their likelihood of causing harm to humans or the environment (class 1, no risk; class 2, low risk; class 3, moderate risk; class 4, high risk). This classification determines the level of containment required (levels 1, 2, 3, and 4, respectively) — and each gene therapy medicinal product must undergo a risk assessment.7

The risk level assigned to an individual gene medicine will depend on its composition, ability to replicate and biological specificity. however, it should be noted that the hazards gene medicines pose to the environment and staff are likely to be less than those posed by some of the infectious organisms already in the hospital environment.

Some gene therapy products require special precautions to ensure they remain biologically active and free from contamination. ideally, gene medicines should be handled in dedicated pharmacy aseptic units by staff who have been trained in the relevant aseptic techniques, and this training should be documented.

Gene therapy products are often presented in very small volumes, which require multiple dilutions before administering to the patient. (viral products are quantified as viral particle units [pUs] or plaque-forming units [pFUs], for example a product may be available in a strength of 1.2 × 10^3 PFU/ml.) therefore, if dilution or part vials need to be administered it is essential that calculations are recorded and checked for accuracy. Gene therapy medicinal products usually require storage in refrigerators (−4C) or freezers (−20C or −80C).

practice guidance

The European Association of Hospital Pharmacists has published guidance on the safe handling of gene medicines, to help hospital pharmacies prepare for gene therapy products becoming available as licensed medicines.9 The guidance provides broad and practical recommendations for handling gene medicines in clinical practice and facilitating practitioners’ acceptance and
confidence in working with this new group of treatments. It encompasses advice on storage, transportation, preparation, dispensing, administration, waste disposal, spillage and decontamination, as well as accidental exposure by staff at all stages of handling. The guidance, to be used in conjunction with the summary of product characteristics of the licensed gene medicine (when available), also contains standard operating procedure templates.

References


Nicola Stoner is consultant pharmacist for cancer at Oxford Radcliffe Hospitals NHS Trust.
E: nicola.stoner@orth.nhs.uk