

The Safety of Cell Therapies

Cells as Medicinal Products

The majority of medicinal products contain a chemical or biological substance as their active ingredient, but a small group of products contain as their active constituent live human cells that are delivered into patients with a defined medical disease. Development of cell therapies has only been possible in recent years. In the EU, the [first stem cell therapy was licensed in 2014](#). Such products are classified in the EU as “Advanced Therapy Medicinal Products”, and a range of examples is shown in Table 1. In some cases, these products are applied directly to the site of tissue injury, such as the eye or into a knee joint, whereas others are injected into the bloodstream.

As licensed medicinal products, cell therapies were all developed in accordance with the normal expectations of quality, safety and efficacy that apply to any new medicine. How these products are developed is described in the literature (e.g. [McBlane et al, 2018](#)) and summarised below.

Stem Cells as Medicinal Products

Adult stem cells are a population of cells in the body with capacity to develop into different specialised cells (eg of the blood, brain, liver, muscle, skin etc) via a process called differentiation. This is the natural process by which new cells are made and the body replenishes its tissues.

Laboratory techniques have been developed which allow the differentiation process to be reversed and an existing population of differentiated cells can revert to a stem cell population – such cells may be called “induced pluripotent stem cells” (iPSC). Given this profile, there is an expectation that, when iPSCs are administered as cell therapies, they could differentiate into a variety of different cell types. Several stem cell containing products are approved for medicinal use (see Table 1).

Testing of cell therapies for Effectiveness

When any new medicinal product is being developed, before it is first tested in humans, evidence is needed to show that it is likely to provide benefit to patients: this is so for cell therapies too. This evidence often comes from studies in animals in which a disease-like state is corrected by use of the cell therapy, or from functional studies, using human cells grown under controlled conditions in the laboratory, to show that the therapy can reverse the hallmarks of the disease.

As an example, modified immune cells, chimeric antigen receptor (CAR) T cells from mice, were first shown to cure cancer in mice through binding to a protein, CD19, present on a type of white blood cell - B lymphocytes. These are cells in which a type of cancer, lymphoma, can develop ([Kochendorfer et al 2010](#)). This science underpinned the later development of human CAR T cell therapies that bind to the CD19 protein - and have cured patients with cancer.

Two of these products, Kymriah® and Yescarta®, have attracted much attention as they are reported to have the potential to cure patients who would otherwise have died of cancer. However, their high cost (currently several £100,000's) will limit their use ([Reuters 2019](#); [Times, 2018](#)).

Testing Cell Therapies for Safety

Prior to human use of cell therapies, they are tested to try to ensure they do not cause adverse effects, or that adverse effects are minimised and will be acceptable. The aim of safety testing of cell therapies is the same as that for any other medicinal product: to identify potential harmful effects (toxicities) and to understand them, so that appropriate steps can be taken to protect humans. Protection might involve carefully monitoring patients for early signs of harm, or by having a remedial treatment immediately available.

Cell therapies can be made from the cells or tissues of the patient to be treated (if so they are, *autologous*) or they can be sourced from a human donor who is not the recipient, and these are

called *allogeneic*. Testing human cell products in animals is difficult if they are given to a normal animal, because their immune system is likely to reject them. The design of animal safety studies prior to clinical use may require experimental animals that have an immune-deficiency or are immunosuppressed, to avoid their immune systems rejecting the human cells ([Sharpe, 2018](#)).

Some cell therapies bind to components of cells (targets) which are *only* present in humans. In this case, types of toxicity which result from binding of that cell target cannot be identified in animals. In the example above with CAR T cells, the CD19 antigen in mice is different from the CD19 of humans and so the human cell therapy cannot produce the effect in mice that it does in humans with cancer.

For some cell products, it can be sufficient to assess unwanted effects on vital systems such as the heart, lungs or the nervous system in animals undergoing testing for effectiveness, and these may be the only safety data generated before clinical trials in patients. However, for most cell therapies, specific safety studies are done, including assessment of where in the body the cells go after being administered (called biodistribution), assessing how long the cells persist for in animals, as well as assessing whether toxic effects can arise after administering the cells. Descriptive information on the fate of cells in animals is primarily to help understand any harmful effects in animals, rather than to predict the distribution of cells in humans.

One concern is the possibility that cell therapy could itself cause cancer in the patient ([Sato et al 2019](#)). The possibility that a change in the cells during their manufacture (engineering their DNA) might lead to cancer needs to be considered and the risk assessed before the first human use. To address this experimentally, different methods are used to determine whether there are any abnormalities that might raise concern about cancer inducing property of the cells. Tests can include analyses of the chromosomes of manipulated cells, to see if any abnormalities related to cancer can be recognised; second and third lines of testing can analyse the function of cells (gene expression profiles) to determine whether there is any activation of known cancer causing genes and to test whether cells show uncontrolled growth in the laboratory. In some cases, cell therapies are given to rodents to determine whether a tumour forms.

Clinical Aspects

There is almost no limit to the therapeutic uses proposed for cell therapies: diabetes, Parkinson's disease, heart failure, retinal degeneration, chronic kidney disease, wound healing, stroke and spinal cord injury are among the diseases for which evidence is being amassed to support the use of cells as therapies. The term "regenerative medicine" is sometimes used to describe the action of these products, as the intent is to regenerate the function lost through disease or injury to a tissue. In each case, clinical benefit and safety need to be shown by testing the experimental cell therapy in patients, comparing what happens in patients who get the experimental cell therapy with an equivalent group of patients who do not.

Unfortunately, use of some unproven cell therapies has been associated with serious adverse events including formation of tissue masses at the site of administration, or loss of vision following their administration into the eye ([Bauer et al 2018](#)). In order to try to ensure that such events do not occur, the testing of cell therapies is independently regulated by Government Regulatory Authorities.

Cell therapies are not given to normal healthy volunteers. Their first use in humans is in patients and, as a consequence, even from very first use, although safety is the priority at that stage of testing, there needs to be a reason to expect some benefit to that patient. At the time when a government regulatory authority is asked to approve the use of cell therapy in patients on a commercial basis, the benefit-risk balance should be in favour of the product.

Some cell therapies have the potential to be given as a one-time treatment, whereas others may require repeated administration, either as a course of treatment, or where there is a change in the patient's condition which suggests a need for re-treatment. The optimum way of using each product has to be determined, as is the case for other medicines.

For autologous cell therapy, the patient must provide a tissue sample from which the medicinal product is made, in a process that usually takes a few weeks. This renders the optimal design of a

placebo-controlled and blinded clinical trial impossible, as both the patient and the doctor will know whether they have received the cell therapy or not. In some cases, comparison is made with existing information from similar patients who were not given the experimental therapy (historical controls) as the best way to access the effect of the cell therapy.

In Summary

Cells can be used to treat human patients with serious, sometimes life-threatening medical conditions. A positive benefit-risk judgement needs to be developed for each product. Although currently only a small number of cell therapies have been approved, they can provide revolutionary treatment for some patients.

For products that contain live human cells, the nature of the experimental safety testing which is needed before they are licenced for sale differs from those expected for a conventional medicine. Nevertheless, although the details differ, cell therapies are developed with the same aim; to ensure quality, safety and efficacy, to provide patients with a treatment that is as safe and as effective as possible.

Table 1: Examples of Cell Therapy Products Approved in the UK and EU

Medicinal Product	Description	Therapeutic Use	Route of administration
Alofisel	The patients own stem cells extracted from fat tissue and which have been induced to grow in the laboratory	Treatment of complex anal fistulae in adult patients with inflammatory bowel (Crohn's) disease	For surgical administration into the fistula
Holoclar	Donated cells from the cornea of the eye, containing stem cells, which have been induced to grow in the laboratory	Treatment of patients with moderate to severe deficiency of cornea of the eye.	Injected into the eye, usually under local anaesthesia
Kymriah	The patients own white blood cells (T lymphocytes) genetically modified using a virus to encode a chimeric antigen receptor against CD19, which directs an immune response against the tumour	Treatment of patients up to 25 years with B-cell leukaemia (acute lymphoblastic) Adults with B-cell lymphoma (diffuse large cell)	Intravenous infusion
Spherox	Spheroids of the patients own cartilage-producing cells	Repair of cartilage damage (up to 10 cm ²) in the knee joint	Surgical implantation into the knee joint
Strimvelis	The patients own white blood cells, genetically modified with a virus to correct a mutation in adenosine deaminase gene.	Treatment of severe combined immunodeficiency (due to adenosine deaminase deficiency) when no suitable bone marrow donor is available	Intravenous infusion
Yescarta	The patients own white blood cells (T lymphocytes) genetically modified using a virus to encode a chimeric antigen receptor, which directs an immune response against the tumour	Treatment of lymphoma (diffuse large B-cell or mediastinal large B-cell)	Intravenous infusion
Zynteglo	The patients own bone marrow, genetically modified using a virus to correct a mutation which impairs ability to make normal red blood cells	Treatment of patients 12 years and older with abnormal red blood cells due to a genetic mutation	For intravenous administration

