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Advanced therapy medicinal products in surgery

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Short Report

This work is unfunded and has not been presented at a previous meeting

Word count excluding references 1119
Complex gene, cell or tissue-based solutions are increasingly being used to treat diseases, which have direct relevance to surgery in that they provide alternatives to surgery or require surgical intervention for their delivery. New products are being developed in almost every branch of surgery to correct gene defects, assist tissue repair or regeneration, to treat cancer or to replace damaged tissues or organs. Such products are grouped under the umbrella term advanced therapy medicinal products (ATMP)\(^1\). There are three main product areas considered as ATMPs (Figure 1). Gene therapy based medicines typically involve the delivery of strands of recombinant DNA designed to correct a gene defect. Novel somatic gene editing technologies including clustered regularly interspaced short palindromic repeats–CRISPR-associated proteins (CRISPR-Cas), may also fall under the same classification and regulatory framework as recombinant DNA treatments although the scientific approach and mechanism of action is different\(^2\).

The second, ATMP type is somatic cell therapy medicine products (sCTMP)\(^3\). This describes a therapy based around cells or tissues, which have undergone substantial manipulation so that biological properties, physiology or structural properties have been altered. Also included are products involving cells or tissues where the intention is that they will not be used for the same functions in the recipient as they were in the donor. In both cases the products are intended to be administered to humans for the purpose of treating, preventing or diagnosing disease through the action of its cells. Many stem cell therapies and chimaeric antigen receptor T cell (CAR T cell) therapies fall within this category sCTMP.

The third type of ATMP is tissue-engineered medicinal products. This covers products such as decellularised scaffolds and also products where cells are combined with a matrix or scaffold. In the case of both somatic cell therapy medicine products and tissue engineered medicines cells are often derived from the patient and modified before being given back in an immunologically autologous fashion. Tissue engineered products may use allogeneic material or animal tissue which has been treated to remove HLA antigens for example skin, bone or cartilage scaffolds.

All ATMPs should be supported by robust research evidence base which depending on the specific ATMP in question may require large animal studies. Unfortunately some of the early developments in ATMPs did not comply with existent research governance and regulatory steps and have caused harm to patients. Notable cases of patient harm have arisen through attempts at tracheal transplantation leading to fatalities\(^4,5\) and unregulated ocular injection of stem cells leading to blindness\(^6\). It is critically important that surgeons involved in this space fully understand their roles and responsibilities within the regulatory frameworks designed for the safe administration of ATMPs and that patients are properly protected.

Responsibility for regulation of ATMPs falls under the European Medicines Agency (EMA) in Europe and under the Food and Drug Administration in USA. In the United Kingdom regulation is also subject to the Medicines...
Healthcare Regulatory Authority MHRA and will be subject to equivalent national regulation in other European countries. There are multiple areas where surgeons may be involved in the development pathway of ATMPs (Figure 2). In the United Kingdom the acquisition of cells or tissues from a donor, whether this is for an autologous or allogeneic ATMP must be conducted under the Human Tissue Act and with written informed consent of the donor or in the case of a deceased donor with family assent. Such consent or assent should include details of the intended use of the cells or tissues and their final destination. If cells or tissues are being removed for commercial development of an ATMP then this should also be made clear to the donor. Responsibility for taking consent and ensuring that appropriate HTA approvals are in place may sit with the surgeon undertaking the procedure. Collection of cells or tissues should be performed following a standard operating procedure which maintains adopts aseptic practice, maintains sterility through transfer or storage and which seeks to optimize the condition of material removed for ATMP production. The handling of cells or tissues removed in the operating theatre are also likely to involve the surgeon who should be fluent with the appropriate protocols. Cells or tissues may require storage or transfer and this should also be covered by a standard operating procedure to ensure a safe chain of custody of the material to the laboratory or local storage and under optimal conditions as required.

Manipulation of cells or tissues in the United Kingdom must be undertaken in a Good Manufacturing Process compliant laboratory, which has been designated for this purpose. This is to ensure that ATMP are manufactured to the best possible standards under a regulatory framework and specifically avoiding risks such as cross contamination of cells or microbiological contamination, which could have potentially devastating consequences for the recipient. Some tissue engineered products may be manufactured using a scaffold which is specific to the recipient and which requires the involvement of a surgeon in design of a scaffold for example facial reconstructive surgery. Once the manufacture of an ATMP has been completed and has completed quality assurance checks it is issued to the clinical area. Consent of the recipient must be fully informed and should discuss alternative treatments as well as the option of no intervention. Known and theoretical risks should be discussed with recipients and this again may fall within the responsibility of the surgeon. Administration of the ATMP should follow a standard operating procedure, which maintains asepsis and optimizes the conditions for delivery of the ATMP. Equally any supporting staff involved in the administration or surgical delivery of an ATMP must be fully aware of the SOP and conditions for it’s administration. The manufacture and administration of many ATMPs is complex and involves scientists, pharmacists, regulators, clinical administration and other clinicians in addition to surgeons. Finally the surgeon has a responsibility to follow up patients treated with an ATMP and to report and manage any adverse events which might be related to the ATMP or surgery required for it’s administration.

The development of novel ATMPs whether they be gene therapy or stem cell or other cell therapy products either alone or in combination with scaffold, matrices or other materials represent an exciting and innovative area of
science. This new branch of medicine is expanding rapidly and has the potential to offer hope to patients in a number of difficult-to-treat diseases. Surgeons will be expected to play significant roles in the acquisition of cells and tissues for ATMP manufacture, assisting in ATMP design in certain circumstances and probably most frequently in the delivery or administration of ATMPs to patients. It is critical that the surgical community is aware of the regulatory framework, which exists to maintain the quality and safety of ATMP and to protect patients from harm. Similarly it is important that surgeons fully understand their role, how this will interact with others in the ATMP manufacturing and delivery pathway and their responsibilities to patients.

References


8. Living donor organ or tissue donation

9. Deceased donor organ and tissue donation
Figure Legends

Figure 1.

Classification of advanced therapy medicinal products ATMPs with examples and example applications

Figure 2.

Manufacturing pathway of advanced therapy medicinal products ATMPs. Blue boxes indicate where surgeons are most likely to be directly involved in the pathway.
<table>
<thead>
<tr>
<th>Advanced therapy medicinal products</th>
<th>Example</th>
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<tr>
<td>Gene therapy</td>
<td>Genetic modification of gene associated with disease</td>
<td>Correction of single gene defect retinal disease</td>
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<tr>
<td>Somatic cell therapy</td>
<td>Human mesenchymal cells used to promote healing</td>
<td>Cartilage repair</td>
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<tr>
<td>Tissue engineered medicines</td>
<td>Decellularised scaffold or scaffold containing autologous or allogeneic modified cells</td>
<td>Skin repair burns, Diabetic ulcer healing</td>
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Classification of advanced therapy medicinal products ATMPs with examples and example applications

237x126mm (150 x 150 DPI)
Manufacturing pathway of advanced therapy medicinal products ATMPs. Blue boxes indicate where surgeons are most likely to be directly involved in the pathway.

124x159mm (150 x 150 DPI)