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**New era of personalized medicine: Advanced therapy medicinal products in Europe**

García-González J *et al*. Advanced therapy medicinal products in Europe

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**Abstract**

Advanced therapy medicinal products are human medical therapies based on genes, cells, or tissues, and due to their characteristics, they offer new innovative opportunities for the treatment of diseases and injuries, especially for diseases beyond the reach of traditional approaches. These therapies are at the forefront of innovation and have historically been very controversial, although in the last decade they have gained prominence while the number of new advanced therapies has increased every year. In this regard, despite the controversy they may generate, they are expected to dominate the market in the coming decades. Technologies based on advanced therapies are the present and future of medicine and bring us closer to the long-awaited precision medicine. Here we review the field as it stands today, with a focus on the molecular mechanisms that guided the different advanced therapies approved by the European Medicines Agency, their current status, and their legal approval.

**Key Words:** Advanced therapy; Advanced therapy medicinal products; Cell therapy; Gene therapy; Tissue therapy; Chimeric antigen receptor T cell

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**Core Tip:** The advanced therapy medicinal products (ATMPs) have opened a new world of possibilities in the prevention and treatment of a large number of diseases that have not been effectively treated to date. ATMPs are based on the use of novel and sophisticated technologies adapted to each patient (personalized medicine), as well as on the discovery of novel and reliable biomarkers for the prediction and monitoring of clinical response. In this work we describe the latest advances in ATMPs approved by the European Medicines Agency, the molecular mechanisms that guided their medical benefits, how they work, the current status, and how they can change the medicine field forever, approaching precision personalized medicine.

**INTRODUCTION**

Recent advances in biomedical and biotechnology research have opened new challenges and promising prospects for the development of advanced therapies in human diseases that could potentially have a major impact on patients' cure expectations, quality of life, and public health[1]. The term ’advanced therapies‘ includes new therapeutic strategies, based on the use of novel and sophisticated technologies tailored to the patient (personalized medicine), as well as novel and reliable biomarkers being discovered for prediction and the monitoring of clinical response[2]. However, the regulatory issues to be addressed in the clinical development of these new therapies are much more complex compared to traditional discovery of new drugs[3,4]. As a consequence, the process of translating clinical trials with advanced therapies into clinical practice is complex, due to the high personalization and because health systems may not be prepared for the impact of these therapies[5]. Nowadays, a paradigm shift is taking place in healthcare related to advanced therapy medicinal products (ATMPs) due to the enormous potential of these therapies to prevent and treat many diseases. As most of these therapies are almost entirely personalized, they carry high development and manufacturing costs[6], strict regulatory requirements[7], reimbursement challenges[8], and complex intervention procedures[9]. These intrinsic characteristics make the therapeutic benefit just one of the many factors necessary to consider in successfully commercializing the therapy. Approvals of new ATMPs are expected to increase dramatically in the coming decades, opening up a whole new range of ethical, therapeutic, legal, and financial issues. To date, 15 advanced therapies have been approved by the European Medicines Agency (EMA), while only 10 have obtained authorisation to market them (Table 1). The other 5 ATMPs were withdrawn or discontinued by their manufacturers and removed from the market.

**ATMPs in Europe**

Advanced therapy drugs offer new and innovative opportunities for the treatment of diseases and injuries that are currently incurable. Actually, ATMPs can be classified into three main types: gene therapy medicines, cell therapy medicines, and tissue-engineered medicines. However, some ATMPs may contain one or more different therapies as an integral part of the medicine; these are referred to as combined ATMPs.

**Gene therapy**

Human gene therapy involves inserting missing functional elements into an individual's genome. Gene therapy seeks to attain long-term expression of the gene of interest to cure or attenuate the symptoms of the disease, avoiding unfavourable events or trying to minimize them. Gene therapy can be performed *in vivo* or *ex vivo*. *In vivo* gene therapy consists of the administration of genes directly to the patient, similar to the traditional administration of other types of pharmaceutical agents. In contrast, for *ex vivo* transduction, cells are removed from the patient and transduced with the gene of interest in the laboratory. The cells are then returned to the patient in specific procedures, usually similar to those used in haematopoietic stem cell transplantation (HSCT).

***Glybera®***

Glybera (Alipogene tiparvovec) is a gene therapy medicinal product (GTMP) for patients with familial lipoprotein lipase deficiency, who suffer severe or multiple pancreatitis attacks despite following dietary fat restrictions. Glybera contains a variant of the human lipoprotein lipase gene *LPLS447X* in order to resolve the enzyme deficiency[10].

The vector used comprises a protein shell derived from adeno-associated virus serotype 1 (AAV1), the Cytomegalovirus promoter, a woodchuck hepatitis virus posttranscriptional regulatory element, and AAV2-derived inverted terminal repeats. It is administered as one-time series of intramuscular injections in the legs where myocytes from the muscle fibers are transduced by the virus and LPL enzyme is expressed[10].

Glybera is an orphan drug and UniQure received authorisation from the EMA in October 2012. However, this authorisation, valid for 5 years, expired in October 2017 and the owner decided not to renew it due to the limited use and low demand for this therapy.

***Imlygic®***

Imlygic (talimogen laherparepvec) is an oncolytic herpes simplex virus type 1 (HSV-1) genetically manipulated and developed to treat multiple melanoma-related solid tumours[11].

This drug was developed by Amgen and approved in December 2015. It is indicated for the treatment of adults with metastatic unresectable melanoma with regional or distant involvement and without bone, brain, lung, or other visceral metastases. Although the incidence of metastatic unresectable melanoma is unclear, the current incidence of melanoma is estimated to be around 26/100000 people[12].

This therapy is based on oncolytic immunotherapy derived from HSV-1, which has been modified to replicate within tumours and produce the human granulocyte macrophage-colony stimulating factor (GM-CSF) immune-stimulating protein. Imlygic causes tumour cell death and the release of tumour-derived antigens[13]. Together with GM-CSF it promotes a systemic anti-tumour immune response and an effector T-lymphocyte response. While the antiviral immune response protects normal cells after Imlygic infection, tumours have been shown to be susceptible to injury and cell death caused by HSV-1 viruses deficient in *ICP34.5*, including Imlygic. *ICP47* suppression prevents the negative regulation of antigen-presenting molecules and increases the expression of the HSV gene *US11*, thus increasing viral replication in tumour cells.

***Strimvelis®***

Strimvelis is a gene and cell therapy that is based on CD34+ cells transduced with retroviral vector in order to encode the human adenosine deaminase (ADA), and, it was the first approved *ex vivo* stem cell gene approved by the EMA[14]. Specifically, Strimvelis was approved for the treatment of people who suffer severe combined immunodeficiency due to an adenosine deaminase deficiency (ADA-SCID)[15]. ADA-SCID accounts for 10%-15% of all SCID cases. Its annual incidence is estimated at 1/200000-1000000, and Strimvelis has been designated an orphan drug. After several collaborations between hospitals and pharmaceutical companies, in April 2018 Orchard Therapeutics became the marketing authorisation holder of Strimvelis.

To prepare Strimvelis, a sample of a patient's bone marrow is needed, from which CD34+ cells are collected. Subsequently, the CD34+ cells are transduced with a retroviral vector encoding the cDNA sequence of ADA enzyme. After perfusion, CD34+ cells are grafted into the bone marrow, where regeneration of the hematopoietic system occurs with cells expressing active levels of ADA enzyme. The patient receives only one administration for life. It was authorised by the EMA in May 2016[16].

***Kymriah®***

Kymriah (tisagenlecleucel) is an immunocellular treatment consisting of autologous T cells genetically modified *ex vivo* using a lentiviral vector encoding anti-CD19 chimeric antigen receptor (CAR). The CAR consists of a single-chain antibody fragment of murine origin that recognizes CD19 and binds to CD137 and CD3 zeta. CD3 zeta is very important for initiating T-cell activation and therefore antitumor activity, and CD137 acts by increasing the persistence and expansion of treatment. CAR works by promoting T cell expansion and binding to CD19-expressing cells, ensuring treatment effectiveness[17].

This treatment involves a single administration that reprograms the cells of the immune system; therefore, the cellular composition and the final number of cells are different for each patient. In addition to T cells, Natural Killer cells may also be present. Kymriah is a CAR therapy developed by Novartis, with an orphan drug designation, due to the prevalence of 1-5/10000[18]. It was approved by the EMA in August 2018 for two different therapeutic indications, acute lymphoblastic leukaemia and diffuse large-cell B lymphoma (LBDCG).

***Yescarta®***

Yescarta (axicabtagene ciloleucel) is a genetically modified autologous T cell immunotherapy directed against CD19[19]. To prepare Yescarta, the patient's T cells are extracted and genetically modified *ex vivo* by retroviral transduction to express a CAR, which is comprised of a murine anti-CD19 fragment linked to the CD28 stimulatory domain and the signalling domain CD3-zeta. Once anti-CD19 CAR-T cells bind to CD19-expressing target cells, the CD28 and CD3-zeta stimulatory domains activate signalling cascades, leading to activation, proliferation, acquisition of effector functions and inflammatory cytokines and chemokine secretion[19]. These events induce apoptosis and necrosis of CD19-expressing target cells. Viable anti-CD19 positive CAR cells are expanded and re-perfused into the patient, where they recognize and eliminate CD19-expressing target cells. Yescarta was designated as therapy for people who suffer from relapsed or refractory diffuse large cell B lymphoma and primary mediastinal B-cell lymphoma, if they were previously treated with two or more lines of systemic treatment. Yescarta obtained EMA approval in August 2018[20,21]. Yescarta is a CAR therapy developed and marketed by Gilead, with an orphan drug designation.

***Luxturna®***

Luxturna (voretigene neparvovec) is a GTMP indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy, a rare genetic disease associated with biallelic *RPE65* mutations[22]. Luxturna was the first FDA-approved drug for gene therapy *in vivo* to use recombinant adeno-associated viruses as vectors[23].

This therapy can only be used while patients have enough functional retinal cells and when retinal dystrophy is mediated by a mutated *RPE65* gene, that encodes the trans-retinol isomerase, necessary for the normal functioning of retinal cells in the visual cycle[20].

Luxturna is composed of a virus that contains normal copies of *RPE65* gene. This treatment is injected into the subretinal space where the virus delivers *RPE65* gene to the retinal pigment epithelial cells that express the missing enzyme. This contributes to improving the functioning of retinal cells by the biological conversion of a photon into an electrical signal, slowing down the progression of the disease[20,24].

Inherited retinal dystrophy is a low-prevalence disease, and Luxturna was designated an orphan drug for retinitis pigmentosa in July 2015, and for Leber congenital amaurosis in April 2012. Novartis is the current marketing authorisation holder[25].

***Zalmoxis®***

Zalmoxis is a GTMP based on allogeneic T cells. These cells are genetically modified with a retroviral vector encoding a truncated form of the low affinity human nerve growth factor receptor and the herpes simplex I virus thymidine kinase[26].

The approved clinical indication is as a complementary treatment in adults who have received a HSCT from a partially matched donor (haploidentical transplant). Before receiving an HSCT, the patient must be treated to eliminate existing bone marrow cells, including cancer cells and immune cells. Zalmoxis is administered to restore the patient's immune system after transplant[26]. Zalmoxis was designated an orphan drug in October, 2003.

Zalmoxis T cells sometimes attack the patient's body causing problems for the host. To avoid this problem, the suicide gene was introduced, which makes the patient susceptible to Ganciclovir or Valganciclovir, so if it ends up causing a problem for the host, it is treated with these complementary drugs, which act by killing the T cells that have the suicide gene.

Zalmoxis was developed by MolMed; in August 2016 the EMA granted its conditional approval. Because Zalmoxis addresses an unmet medical need, approval was granted in the interest of public health as the benefit of immediate availability outweighed the risk of less complete data than is normally required. Nevertheless, Zalmoxis was withdrawn in February 2020.

***Zynteglo®***

Zynteglo (betibeglogén autotemcel) is a marketed gene therapy medicine for the treatment of β-thalassaemia in patients from 12 years of age that do not have the genotype β0/β0, for whom haematopoietic progenitor cell transplantation (HPC) is appropriate but a HPC donor with a human leukocyte antigen system compatible is not available[27]. Beta-thalassaemia is characterized by the deficiency (β+) or absence (β0) of the synthesis of the beta-globin chains of haemoglobin. The prevalence is estimated at 1/100000 worldwide; thus, Zynteglo is an orphan drug.

First, haematopoietic stem cells (HSCs) are collected from the patient, and then functional copies of the modified β-globin gene are added through the transduction of autologous CD34+ cells with the lentiviral vector BB305. After perfusion, the transduced CD34+ HSCs are implanted into the bone marrow to produce red blood cells with biologically active β-globin, which will combine with α-globin to produce functional haemoglobin[28]. The EMA granted conditional marketing for Zynteglo in May 2019. The marketing authorisation holder is Bluebird Bio.

***Zolgensma®***

Zolgensma (onasemnogene abeparvovec) is a gene therapy used to treat spinal muscular atrophy (SMA), a pathology that affects the nerves and induces muscle wasting, weakness and paralysis[29]. It is given to patients who have inherited mutations related to *SMN1* genes, which play a central role in the normal functioning of the nerves that control muscle movements. Additionally, eligible patients must have been diagnosed with SMA type 1 or have up to 3 copies of *SMN2 gene*.

Zolgensma is based on a single administration through an intravenous infusion. SMA is a childhood illness with an incidence of approximately 1/10000, with 45%-60% of cases being diagnosed as SMA Type 1[30]. Zolgensma was designated an orphan drug in June 2015. However, the EMA only recently authorised its marketing to the manufacturing company AveXis EU Limited, on May 18, 2020[30]. Furthermore, Zolgensma is the most expensive gene therapy on the market (€2 million for a one-time treatment)[31].

The various gene therapies are summarized in Table 1.

**Cell therapy**

Cell therapy involves the introduction of new cells into a tissue to address a medical condition. Usually cells reintroduced into patients have been genetically modified or cultured with recombinant proteins to add a gene/protein for therapeutic effect. Cell therapies can be autologous (cells obtained from the patient) or allogeneic (from another patient).

***Provenge®***

Provenge (Sipuleucel-T) is a cell-based cancer immunotherapy for prostate cancer. It is a personalized treatment that works by programming the immune system of each patient to destroy cancer cells[32]. Prostate cancer is the second most frequent malignancy in men worldwide, representing 1276106 new cases and causing 358989 deaths in 2018[33].

Provenge consists of autologous peripheral blood mononuclear cells (PBMCs) treated by leukapheresis, in which white blood cells are separated from blood and activated with prostatic acid phosphatase (PAP) linked to GM-CSF (PAP-GM-CSF). The patient’s PBMCs are cultured (activated) with a recombinant human protein (PAP-GM-CSF), and re-injected into the patient three times over 2 wk[34].

PAP is an enzyme produced by prostate tissue that is over-expressed in this type of cancer; it therefore acts as a specific target for tumour cells. This immunotherapy activates the patient's immune system through his antigen-presenting cells that are cultured *ex vivo* with a fusion protein formed by the linking of PAP and macrophage and granulocyte colony stimulating factor (GM-CSF). Once activated, the antigen-presenting cells acquire the recombinant antigen and, finally, antigen-specific T cells carry out the immune response to PAP-overexpressing tumour cells[35].

Provenge marketing authorisation was granted for the European Union (EU) in September 2013 to Dendreon UK Ltd. However, in May 2015, the European Commission withdrew the authorisation.

***Alofisel®***

Alofisel (darvadstrocel) is a cell therapy that consists of expanded adipose stem cells (eASC) used to treat complex anal fistulas in Crohn’s disease patients. Alofisel is used only in cases in which conventional or biological medicine has failed[36].

eASCs have immunomodulatory and anti-inflammatory effects on inflammation sites. Following injection of eASC into the inflamed area, inflammatory cytokines (specifically interferon-γ released by activated immune cells) activate the eASC. The immunoregulatory activity decreases inflammation, which allows the healing of tissues that surround the fistula[37]. Alofisel is another orphan drug, and was developed by Instituto Carlos III in Madrid in collaboration with Tigenix. Currently, Alofisel is commercialized by Takeda; the commercial authorisation was granted in 2017.

The various cell therapies are summarized in Table 1.

**Tissue-engineered medicines**

Tissue therapy consists of the combination of cells, engineered methods, materials (scaffolds) and biochemical (growth factors), and physical-chemical elements for enhancing or replacing biological tissues.

***Chondrocelect®***

ChondroCelect is a tissue engineered product that involves the implantation of autologous chondrocytes taken from the patient's own knee[38]. It is indicated for the treatment of adults with unique symptomatic cartilage defects in the femoral condyle of the knee[38].

First, a biopsy of cartilage from the patient's knee is obtained. The chondrocytes are then cultured and expanded in the laboratory in order to generate enough cells to prepare a cell suspension to be used to treat the cartilage injury. During knee surgery, the suspension is implanted into the patient's injured cartilage. Then, a biological membrane seal is made to retain the cells.

ChondroCelect was the first cell-based product approved in Europe. It received marketing authorisation in October 2009, but it was only marketed in Spain, Belgium, and Netherlands. However, the manufacturers decided to withdraw it from the EU market in 2016[39].

***MACI®***

MACI is an advanced medical product based on a matrix of autologous cultured chondrocytes[40] used to repair cartilage defects of the knee joint.

It consists of 14.5 cm2 porcine collagen membranes that contain the patient's own cartilage cells, which are used to fill the spaces of the damaged cartilage. MACI is used with an area between 3 and 20 cm2 in adults who suffer symptoms such as pain and mobility problems in the knee.

First, a sample of cartilage cells (chondrocytes) is obtained from the patient's joint and cultured in a laboratory. When a sufficient number of cells are obtained, they are placed on the collagen membrane. About 6 wk later, the surgeon adjusts the membrane to the damaged area in the cartilage of the knee and then implants it using a surgical procedure. To keep the implant in place, a fibrin sealant made from blood clotting proteins is used.

MACI obtained marketing authorisation from the EMA in 2013, although to date it has only been marketed in Denmark, Greece, and the United Kingdom. Moreover, in September 2014, the MACI marketing authorisation holder closed the EU manufacturing site for the medical product, and as a consequence, the manufacturing site license was withdrawn. The closure was due to commercial reasons[41].

***Holoclar®***

Holoclar is an *ex vivo* expanded autologous corneal epithelial cell treatment used to replace damaged surface cells (the epithelium) of the cornea[42]. Holoclar is used in patients that suffer moderate to severe limbic stem cell deficiency as a consequence of eye burns. Patients who suffer corneal epithelial damage often have not enough limbic stem cells, so Holoclar provides stem cells to help to replace the damaged corneal cells[20].

Treatment consists of a biopsy from the patient’s cornea, and subsequent cell growth in the laboratory. After surgery, the cells repair the corneal epithelium. Once Holoclar is embedded in the eye, the new corneal cells support replacement of the corneal epithelium and the limbal stem cells support the new cells to constantly replace the damaged cornea[20,42].

The European Commission granted marketing authorisation for Holoclar in February 2015. Because limbal stem-cell deficiency is considered rare (prevalence around 0.3361/10000)[43], Holoclar was designated an orphan drug.

***Spherox®***

Spherox is another 'tissue-engineered product' used in the treatment of cartilage problems in the patella of the knee, similar to MACI®[44]. Spherox is made up of chondrocyte spheroid aggregates obtained from the patient[44].

First, a small sample of cartilage is obtained from the patient's knee to be cultured in the laboratory and to prepare a suspension of chondrocyte spheroids. Later, the medical product is applied to the damaged area in the patient's cartilage. Chondrocyte spheroids adhere to cartilage in less than 20 min, and when implanted in the patient, repair knee defects, producing new tissue. However, Spherox is only used when the affected area is no larger than 10 cm².

The two clinical studies conducted with Spherox demonstrated a significant improvement in pain, quality of life, and ability to take part in sports or recreational activities[45].

The EMA approved the commercialization of Spherox in December 2016, and is still commercialized nowadays[46].

The various tissue-engineered medicines are summarized in Table 1.

**CONCLUSION**

We are currently facing significant challenges in converting new findings from recent advances in basic research into advanced therapies, with great potential impact for patients and public health. While competition is the driving force behind basic research, cooperation, coordination, and infrastructure are essential for translational research, especially in the field of advanced therapies where the regulatory framework is still somewhat in place[47]. ATMPs represent new therapeutic principles, which in turn represent greater complexity and mode of action, making it difficult to define the quality of potential trials. In this regard, species specificity linked to physiological differences and tissue histocompatibility makes it very difficult to develop appropriate animal models and design clinical practice in highly sophisticated human clinical trials. In addition, the problem of conducting trials with limited numbers of patients (who may have rare or poorly studied diseases) and the uncertainties in identifying a safe and effective dose must be considered. Nevertheless, ATMPs are playing a key role in the development and application of precision/personalized medicine because they involve the development of treatments and therapies based on the individual needs of patients, adapting them to patient requirements. There is a strong need for strategic cooperation among all major stakeholders (academics, clinicians, experts, patients, and the pharmaceutical industry) to promote the translation of these therapies into clinical interventions and ultimately into clinical practice, for the benefit of patients and public health. However, while the development of a fully patient-friendly therapy may appear to be an advantage, it is also highly controversial, as gene therapy has never been well received by society due to the risks involved and possible complications. Nonetheless, it should be remembered that ATMPs are often subject to strict regulation, sometimes even more so than conventional therapies; therefore, before they reach the market, their safety and effectiveness must be guaranteed. ATMPs have the potential to be the solution for current incurable diseases, bringing us closer to personalized medicine. Although advances in ATMPs are recent, they are continuously evolving, emerging as one of the most popular and fastest growing therapies worldwide. In fact, there are currently more than 1000 clinical trials based on ATMPs worldwide, although only a privileged few manage to reach the market. In this sense, it is expected that 2021 will be a year of great achievements, with several of these therapies reaching the market: JCAR017[47], bb2121[48], Tab-cely[49], and Lenadogene nolparvovec[50].

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**Table 1 Summary of different advanced therapy medicinal products approved by the European Medicines Agency with their approval date and withdrawal date, if applicable**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Advanced therapy medicinal products** | | | | | | | | |
| **Gene therapies** | **EC approval** | **Withdrawal** | **Cell therapies** | **EC approval** | **Withdrawal** | **Tissue-based therapies** | **EC approval** | **Withdrawal** |
| Glybera | Oct-12 | Oct-17 | Provenge | Sept-13 | May-15 | MACI | Jun-13 | Sept-14 |
| Imlygic | Dec-15 |  | Zalmoxis | Aug-16 | Feb-20 | Holoclar | Feb-15 |  |
| Strimvelis | May-16 |  | Alofisel | Mar-18 |  | Spherox | Jul-17 |  |
| Kymriah | Sept-18 |  | Chondrocelect | Oct-09 | Jan-17 |  |  |  |
| Yescarta | Sept-18 |  |  |  |  |  |  |  |
| Luxturna | Nov-18 |  |  |  |  |  |  |  |
| Zynteglo | Jun-19 |  |  |  |  |  |  |  |
| Zolgensma | Mar-20 |  |  |  |  |  |  |  |

EC: European Commission.