ePTRI

European Paediatric Translational Research Infrastructure

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 777554

Paediatric application of ATMPs

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European Biotech Week 2020

The event is part of the European Biotech Week 2020

PART OF EUROPEAN BIOTECH WEEK

INNOVATION IS IN OUR GENES

Advanced Therapy Medicinal Product

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on **advanced therapy medicinal products** and amending Directive 2001/83/EC (Marketing authorization rules)

and Regulation (EC) No 726/2004 (role and function of the European Medicine Agency)

Legal definition

Advanced therapy medicinal product' means any of the following medicinal products for human use:

— a gene therapy medicinal product

— a somatic cell therapy medicinal product

(as defined in Part IV of Annex I to Directive 2001/83/EC)

— a tissue engineered product

Report of ATMP experience

The 2014 EU Commission report on the application of ATMPs, concluded that the Regulation had protected patients from unsound treatments.

However, it also recognised shortcomings and identified actions to help translate scientific progress into medicinal products available to patients.

Outcome of a multi-stakeholder meeting (2016)

Potential candidates for ATMP treatments include severe, untreatable or chronic diseases, and many clinical trials are currently underway in conditions as varied as cancers, cardiovascular diseases, musculoskeletal conditions and immune system disorders.

No specific mention of paediatric patients

Licensed ATMP in Europe (1)

Name	Description	Age
Strimvelis*	An autologous CD34+ enriched cell fraction transduced with retroviral vector for the human adenosine deaminase (ADA),	Paediatric
Luxturna*	Voretigene neparvovec is a viral vector (AAV2) for the human retinal pigment epithelium 65kDa protein (hRPE65) cDNA to the retina.	Adult / Paediatric
Kymriah*	tisagenlecleucel, autologous T cells genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor(CAR)	Adult / Paediatric
Zynteglo*	autologous CD34+cells encoding βA-T87Q-globin gene	Paediatric

Licensed ATMP in Europe (2)

Name	Description	Age
Alofisel*	expanded adipose stem cells (eASC) for anal fistulae treatment	Adult
Holoclar*	Ex vivo expanded autologous human corneal epithelia lcells containing stem cells.	Adult
Imlygic	an attenuated HSV-1 with coding sequence for human GM-CSF for Melanoma treatment	Adult
Spherox	Spheroids of human autologous matrix-associated chondrocytes, Cartilage Diseases	Adult
Yescarta*	axicabtagene ciloleucel, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse	Adult

Licensed ATMP in Europe (3)

Name	Description	Age
~~Zalmoxis~~	allogeneic T cells genetically modified (ΔLNGFR) and (HSV-TK Mut2) in HSCT	Adult
~~Chondrocelect~~	viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	Adult
~~MACI~~	matrix applied characterised autologous cultured chondrocytes	Adult
~~PROVENGE~~	autologous peripheral-blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T)	Adult
~~Glybera*~~	Alipogene tiparvovec viral vector contains the human lipoprotein lipase (LPL)	Adult

Market or science ?

General issues limiting the rate of development for all ATMPs are:

- Regulatory hurdles
- Complexity of the manufacturing
- Lack of long term data for efficacy affecting reimbursement
- Often targeting small population resulting in a high unit cost

Good Manufacturing Practice (GMP)

In late 2017, guidelines specific to ATMPs were published to adapt the GMP framework to novel aspects of these products, such as decentralised manufacture, final product reconstitution at the treatment centre, and release of out-of-specification (autologous) products.

Specific GCP guidelines for ATMPs are now also under revision.

genetically modified organisms (GMOs)

GMOs are typically approved for use separately from the CTA submission, and additional country-specific information is required.

Recent harmonization effort include a question-and-answer document, a good practice guideline, and a common application form adopted by a number of member states, plus a repository of national regulatory requirements on the EC website to describe the different current requirements among member states.

Supporting Actions

The Orphan Drug and the PRIME incentives may result in an increase of the products developed (>17 under examination).

Similarly a substantial number of products (>30) are under development in the USA facilitated by the regenerative medicine advanced therapy (RMAT) designation, and Fast Track Designation (FTD) incentives.

Market or science ?

Given that a large proportion of non-infective diseases affecting children are monogenic inherited pathologies, why there are still so few ATMP developed ?

- Lack of clear druggable targets, lack of understanding of human early development, lack of validated juvenile animal models, ethical and legal restrains on clinical experimentation
- Limited market value due to high cost of development

EPTRI

A concerted action to address at least the scientific hurdles regarding paediatric drug development are addressed by the EPTRI (European Paediatric Translation Research Infrastructure) initiative

Create a Research Infrastructure to connect and coordinate the access to the paediatric specific resources in Europe

Support Paediatric drug development with excellent science and quality methodology

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