The delivery of advanced therapies to patients: challenges and solutions

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THE DELIVERY OF ADVANCED THERAPIES TO PATIENTS: CHALLENGES AND SOLUTIONS

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Introduction

Regenerative therapies are presented as being able to cure the diseases of the XXI century, especially those coming from the degeneration of the aging human body. Their specific nature based on biological materials raises particular challenging issues on how the regulation should frame biomedical innovation for the society's benefit.

Among them, Advanced Therapy Medicinal Products (ATMP) are medicinal products based on genes, cells or tissues. They rely on technical processes called gene therapy, cell therapy or tissue engineering and aim to treat causes of the diseases rather than symptoms only. They cover wide range of diseases such as rare genetic diseases and more common pathologies (cancers, cardiovascular diseases and neurodegenerative conditions). They offer major clinical and economic potential yet not without safety concerns in some cases. The European Union (EU) supports the development of ATMP manufactured at the industrial scale under Good Manufacturing Practices (GMP) with a specific regulation (EC) n°1394/2007 providing their wide access to the European market for European patients. However, although some medicinal products have obtained a European marketing authorisation granted by the European Commission after the opinion of the European Medicines Agency (EMA), they remain far from being fully accessible to European patients in all the EU Member States. Clinical delivery of ATMP within the healthcare systems is a main issue for which we will consider the current challenges and potential solutions.

ATMP's Market Failures

1- European Cases

Products	Chondrocelect	Glybera	MACI	Provenge	Holoclar	Imlygic	Strimvelis	Zalmoxis	Spherox	Alofisel
EMA Classification	TEP	GTMP	Comb. TIP	CTMP	TEP	GTMP	GTMP	CTMP	TEP	TEP
Therapeutic area	Orthopaedics	Gastro- enterology	Orthopaedics	Oncology	Ophtalmology	Oncology	Immunology	Graft vs. host	Orthopaedics	Gastro-enterology
Year of authorisation	2009	2012	2013	2013	2015	2015	2016	2016	2017	2018
Marketing Authorization type	Normal	Normal	Exceptional circumstances	Normal	Conditional	Normal	Normal	Conditional	Normal	Normal
Orphan designaiton	-	Orphan	-	-	Orphan	-	Orphan	Orphan	-	Orphan
Marketing authorization holder	Tigenix (BE)	UniQure (NL)	Vericel (USA)	Dendreon/ Valeant (USA)	Chiesi (IT)	Amgen Europe (NL)	GSK (UK)	MolMed (IT)	CO.DON (DE)	Takeda Pharma (DK)
		Withdrawal	Suspended	Withdrawal						

TEP: Tissue Engineered Product; GTMP: Gene Therapy Medicinal Product; CTMP: Cell Therapy Medicinal Product; Comb.: Combined

2-Consequences

Clinical adoption has been recognized as a main challenge in the field of advanced therapies, for example:

- In policy discourse on the need to facilitate 'Translational medicine' (From bench to bedside approach)
- In relation to the Product's "life cycle"
- "One of the greatest changes to the delivery of medicine in recent times" (Medicine Manufacturing Industry Partnership, Advanced Therapies Manufacturing Action Plan: Retaining and Attracting Advanced Therapies Manufacture in the UK, 2017)
- These highlight the mismatch between existing healthcare delivery mechanisms for drug and devices, and those required for tissue, cell or gene-based products

Challenges and potential solutions

1- Clinical Delivery Issues

- Manufacturing complexity:
  - ✓Highly sensitive (living) tissues and cells, complexity of the manufacturing processes
  - ✓Need for specific skills and training
- Cost of goods (COG): high cost, risk-sharing agreements and data gathering
- Limits of healthcare systems: limited health budget and resources, already busy
- Need for reconfiguring of workflows, patient pathways and professional boundaries
- Managing patients' hopes and hypes
- Supply chain complexities
  - ✓ Manufacturing: on site, expensive bioprocessing equipment…
  - ✓ Transport: often short shelf life if fresh,
  - ✓ Storage: specific equipment

Regulatory requirements

2- Potential Solutions

<u>Specific Advanced Therapy Treatment Centres: the UK example</u>

What?

- Establishment of specialist cell and gene therapy delivery centres
- Started in February 2018 under the coordination of the Cell and Gene Therapy Catapult (£30 millions from UK Government)

How?

- Partnerships between NHS (patient access, clinical and tissue and blood expertise) and industry (investment and manufacturing expertise)
- Consolidation of resources around these centres and coordination

Where?

- Sites already pioneering the development and clinical trials of ATMP, with will to improve expertise in manufacturing and delivery

Why?

- To develop coordinated systems with the necessary skills for at-scale clinical delivery
- To facilitate the establishments of validated standards of quality and safety of ATMP

<u>Decentralisation of manufacturing</u>

A specific role for hematopoietic progenitor cell collection/processing/administering centres and haematological services

Similarities between some ATMP and existing conventional hematopoietic progenitor cell collections/supply chains/grafts and/or haematological treatments

- Potential role in ATMP development but needs to accommodate with new technical, operational and regulatory-issues and requirements
- More adapted to local patient needs and less complicated supply chain requirements, yet workforce and COG need assessment

<u>Centralisation of manufacturing</u>

Establishment of new manufacturing centres, for example:

- Cell and *Gene* Therapy Catapult large GMP manufacturing centre in Stevenage in the UK: £55 millions investment, 100m^2 of clean room space
- YpoSkesi in France: 121 millions euros, 6000m^2 to be expanded

<u>New or enhanced links between stakeholders</u>

- Enhanced coordination between regulatory agencies and reimbursement bodies early contact with regulators favoured at EU and UK levels

Conclusion

- Governments actively engaged in facilitating innovation of advanced medicines, and clinical delivery identified as a key challenge
- Possible complementarity of presented potential solutions that need to address issues which traverse regulatory, scientific, logistical and social concerns.
- Dual trends of both centralisation and decentralisation of production of advanced therapies
- Decentralized manufacturing of advanced therapies (such as for 3D bioprinting) still under evaluation for cost-effectiveness with the goal of accessibility to more patients
- Preponderance of rare disease targets in the field of authorised ATMP
- Need to consider public health values in advanced therapies policy development, e.g. patients access to advanced therapies via custom-made products in hospitals (Hospital exemption)