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Hurdles in clinical implementation of academic advanced therapy medicinal products: A national evaluation

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Abstract

Background. Since the implementation of the European Union (EU) regulation for advanced therapy medicinal products (ATMPs) in 2009, only six ATMPs achieved marketing authorization approval in the EU. Recognizing the major developments in the ATMP field, starting mostly in academic institutions, we investigated which hurdles were experienced in the whole pathway of ATMP development towards clinical care. *Methods.* Quality interviews were executed with different stakeholders in The Netherlands involved in the ATMP development field, e.g. academic research groups, national authorities and patient organizations. Based on the hurdles mentioned in the interviews, questionnaires were subsequently sent to the academic principal investigators (PIs) and ATMP good manufacturing practice (GMP) facility managers to quantify these hurdles. *Results.* Besides the familiar regulatory routes of marketing authorization (MA) and hospital exemption (HE), a part of the academic PIs perceived that ATMPs should become available by the Tissues and Cells Directive or did not anticipate on the next development steps towards implementation of their ATMP towards regular clinical care. The main hurdles identified were: inadequate financial support, rapidly evolving field, study-related problems, lacking regulatory knowledge, lack of collaborations and responsibility issues. *Discussion.* Creating an academic environment stimulating and planning ATMP development and licensing as well as investing in expanding the relevant regulatory knowledge in academic institutions seems a prerequisite to develop ATMPs from bench to patient.

Key Words: *Biomedical research, Cell- and tissue-based therapy, Clinical trials as topic, Genetic therapy, Therapies, Investigational, Tissue engineering, Translational medical research*

Abbreviations: ATMP, Advanced Therapy Medicinal Product; CAT, Committee for Advanced Therapies; CTA, Clinical Trial Authorisation; CTMP, Cell Therapy Medicinal Product; DC, Dendritic Cells; DCS, Dutch Cancer Society (KWF Kankerbestrijding); EMA, European Medicines Agency; GTMP, Gene Therapy Medicinal Product; HE, Hospital Exemption; HTA, Health Technology Assessment; IP, Intellectual Property; MA, Marketing Authorization; MSC, Mesenchymal Stromal Cells; NK, Natural Killer; PI, Principal Investigator; TEP, Tissue-Engineered Products; TPP, Target Product Profile; ZonMw, Netherlands Organisation for Health Research and Development.

Introduction

The field of cell therapy, gene therapy and tissue-engineered medicinal products (CTMPs, GTMPs and TEPs) is innovative and evolving rapidly [1]. However, only 14 products have applied for marketing authorization (MA) in Europe, from which six have received MA approval [2]. Since 2009, the European Union regulation (EC) No. 1394/2007, specific for these so-called advanced therapy medicinal products (ATMPs) has in effect [3]. A Committee for Advanced Therapies was established by the European Medicines Agency (EMA) for ATMP classification, scientific advice procedures and evaluation of the MA applications [4–11]. Since then, 165 ATMP classification procedures have been performed, 172 Scientific Advices have been issued [2], and considerably more ATMP (pre)clinical trials have been performed [6]. On the basis of the numbers provided by the EMA, it seems that ATMP development toward MA application has a low success rate. Besides the standard EMA MA route, the ATMP regulation defines a second route to reach clinical care

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with ATMPs: the hospital exemption (HE) clause. Under the HE, ATMPs can be used for non-routine therapy, manufactured for an individual patient, within the same member state [12]. Although laid out in the EU regulation, the implementation of the HE clause by national authorities differs among individual member states [13].

In the Netherlands, ATMPs manufactured in compliance with Good Manufacturing Practice (GMP) may be eligible for HE therapy after evaluation of quality, safety and efficacy by the Dutch health care inspectorate [13]. HEs can be approved for 1 year and for either 10 or 50 batches [14,15]. Subsequently, it is possible to apply for an extension of the HE [15]. As many as 92 clinical trials and even more preclinical research projects with ATMPs have been performed in the Netherlands so far, and only one MA has been granted for alipogene tiparvovec (Glybera) [16,17]. As of December 2015, applications for HE approval for 11 ATMPs had been submitted [15]. Again, these numbers imply that, also in the Netherlands, the success rate of ATMP development is low.

The aim of this national study was to identify hurdles to ATMP development for clinical care in the Netherlands. For this purpose, experiences by different stakeholders in the field were systematically analyzed. We also investigated what stakeholders perceived brought their ATMP closer to use in regular clinical care after successful clinical trials have shown safety and efficacy.

Methods

Interviews

From grants provided between 2005 and 2013 by the Netherlands Organization of Health Research and Development (ZonMw) and the Dutch Cancer Society (DCS), ATMP projects were selected for interviews. Projects were independently classified as ATMPs according to ATMP regulation 1394/2007 by two authors (LVD and PM, researchers with >5-year experience in ATMP development and manufacturing). Projects aiming for at least a phase I clinical trial with an ATMP were selected. In the second and third quarters of 2014, qualitative interviews were conducted with the corresponding 29 academic principal investigators and project leaders (PIs), from 10 institutions. During the interviews, 45 ATMPs were discussed.

In addition to the PIs, other stakeholders were selected on the basis of their role in the path of ATMP development toward regular clinical care: authorities covering regulatory affairs, health technology assessment (HTA), health insurance or patient representation, ATMP GMP facility managers and small or medium-sized enterprises. Qualitative interviews with these stakeholders were conducted in the first half of 2015.

To create an open interview setting, the interviews were not recorded. Objectivity was ensured by conducting the interviews with two or three of the authors in attendance (LVD, PM, and SdW). The documented interview summaries were conducted by LVD and reviewed by the other two authors (PM, SdW, or both). All answers were considered to be personal opinions from the individual persons interviewed, unrelated to the formal position of their employers or to the opinion of the authors who conducted the interviews.

The two key questions for all interviews, asked as open questions, were, for both the PIs and the other stakeholders: "How should an/your ATMP be implemented in regular clinical care after successful clinical phase I/II trials?" and "What are the main hurdles experienced during development and implementation of an ATMP?"

Questionnaires

The hurdles mentioned in the interviews were objectively documented and classified into sub-hurdles see Table I. Subsequently, these hurdles were adopted in digital questionnaires to be able to further quantify the relevance of these hurdles for the academic PIs and the ATMP GMP facility managers, both directly involved in the development of ATMPs (see Supplementary Table S1). Each Dutch ATMP GMP

Table I. Hurdles in ATMP development with sub-classification.

Hurdles	Subclassification
Financial support	Phase IV trials
	Phase III trials
	MA
	Phase I/II trials
	Reimbursement
	Employees training
	HE
	Preclinical trials
Regulatory knowledge	EMA documentation
	MA
	Clinical trials and HE Documentation
	Drug development
	IP
Rapid evolving field	Modify product
	New innovative treatments
Study-related problems	Starting materials
	Patient recruitment
	Publication rate
	Control group
	Employees
Collaboration and responsibility	Other companies
	IP responsibility
	Other departments