ECL ACCESS TO MEDICINES TASK FORCE

THE POTENTIAL FOR ACADEMIC DEVELOPMENT OF MEDICINES IN EUROPE

Case study of advanced therapy medicinal products

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ABOUT THE ECL ACCESS TO MEDICINES TASK FORCE

Established in 2016, the ECL Access to Medicines Task Force aims to make safe and effective medicines available to all cancer patients in Europe, by insisting on accessibility, availability, affordability, and increased transparency related to medicine prices, ultimately leading to sustainability of healthcare systems. The Task Force strongly believes in the power of constructive dialogue. We urge all stakeholders to push for accessibility to high-quality treatments, improving both survival and the quality of life of cancer patients. ECL Task Force connects 31 national and regional cancer societies in 26 European countries, representing over 500 million Europeans.

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FOREWORD

Both medical and technological developments have led to the increased provision of cancer medicines on the market. These improved and advanced treatments make it possible for cancer patients to live longer with a better quality of life.

Unfortunately, the number of people diagnosed with cancer is rising every year. A new case of cancer is diagnosed in the European Union every 9 seconds. Many of these patients need innovative therapies. However, there are many hurdles to making these treatments quickly available to every new patient.

Currently, the only way to bring innovative therapies to patients is via a commercial route, but the prices are extremely high, and for advanced therapy medicinal products (ATMPs), they range from €300,000 to more than €1,000,000. Moreover, the pharmaceutical industry is highly unlikely to invest in therapies that will not ensure a return on investment, even if for some patients the therapy can be lifesaving.

With this paper, we aim to explore how academia can contribute to the development of innovative treatments and improve their access for cancer patients at a fair price. Four case studies of academically developed cell and gene therapies will be analysed. Following that, recommendations for an academic-driven pathway for the development of cancer medicines will be put forward.

We are convinced that academically developed innovative therapies have an important role to play in cancer care, and that commercial treatments alone are not going to solve all medical needs.

Steering Committee of the ECL Access to Medicines Task Force

ECL ACCESS TO MEDICINES TASK FORCE

EXECUTIVE SUMMARY

In Europe, around 2.7 million people are diagnosed with cancer every year – and this number is set to grow. Many of these cancer patients have unmet medical needs, meaning that there are no targeted or only limited treatment options for them. Fortunately, innovative therapies, such as the advanced therapy medicinal products (ATMPs) offer ground-breaking new opportunities for the treatment of their disease.

European Commission's ambition to provide all patients with timely and equal access to affordable, high-quality, effective and safe medicines, as envisioned in the Pharmaceutical Strategy for Europe, is well aligned with the goals of the ECL Access to Medicines Task Force. This paper spotlights the role of academia in developing the ATMPs, as the standard pathway through commercial development by pharmaceutical industry is not always suitable, because not all such therapies are commercially viable.

The paper analyses four case studies illustrating academic development of innovative cancer therapies and highlights main bottlenecks that hinder such pathway of bringing medicines to those in need. It concludes that parallel to the commercial development of the ATMPs by the pharmaceutical companies, academia has a clear role to play when it comes to the development of personalised treatments and therapies for rare, paediatric disorders or diseases, provided that identified challenges are overcome. To that end, the paper outlines key recommendations for regulators, funding bodies, academics, and Health Technology Assessment (HTA) bodies to facilitate the non-commercial pathway of medicines development in Europe.

RECOMMENDATIONS

We put forward the following recommendations to support academic development and to bring treatments to patients quicker.

Regulatory framework

- **There is a need for a non-commercial academic pathway to the patient, leading to an authorisation by the EMA. This is important to make ATMPs available to patient groups with high unmet needs.** This includes an academic registration trajectory, with lower or no regulatory fees; some regulatory flexibility to take the very small patient populations and the intricate complexity of niche and personalised treatments into account, support to academics to fulfil the procedures and requirements. This process should lead to treatments that **are as qualitative, safe and effective as treatments** sprouting from the traditional commercial pathway. We highly encourage the development of the current EMA pilot for ATMP development further into a formal pathway.
- Limitations to implement a new ATMP in clinical practice by academia need to be alleviated to **ensure access across the EU**. Fees for marketing authorisation and reimbursement procedures need to be lowered or waived for academia. Academic authorisation licenses should be valid in all EU Member States without export issues.
- For personalised treatments or niche ATMPs for ultra-rare diseases and other exemption situations, the Hospital Exemption (HE) remains necessary. However, because there are countries which use it in different ways, there is need for some harmonisation of the adoption at a centralised level of some operational criteria that have proven to work at the national level (13). **The treatment under HE should be accessible for every European patient in need of the product**. Data should be collected to monitor outcomes, but not necessarily to build a dossier for marketing authorisation, as niche products are likely to fail in a commercial setting or meet the needs of only a few patients. An unlevel playing field can be avoided by using the commercial marketing authorisation pathway, the non-commercial academic authorisation pathway, and the HE in a complementary fashion. They should be parallel to each other without overlap, for the purposes of commercial development, non-commercial development, and exemption situations, respectively. Current HE licenses that exceed exemption situations should be offered a transition period to obtain an EMA authorisation. These adaptations to the HE would only benefit access if a non-commercial academic pathway is realised.
- European and national authorities should take the specificities of early phase research into account when authorising clinical trials. **Discussions between researchers and regulators** on new developments and how to embed them in the legislation can be very useful. These dialogues are also relevant to adjust the regulatory system to new technological developments, such as closed manufacturing systems and a shift from product regulation to process regulation in relation to clinical outcomes.

Funding

- Funding bodies, HTA bodies, and health insurance funds should ensure that public funding for late phase clinical trials and regulatory procedures is available for break-through ATMPs developed by academia.

Collaboration

- Collaboration among academic hospitals should be stimulated, so that knowledge on topics such as good manufacturing practice (GMP) and quality control, and GMP manufacturing capacity, may be shared. These **academic networks** are also vital in making treatments available across Europe and in setting up international clinical trials.
- The Clinical Trials Regulation facilitates a harmonised and more efficient system for clinical trial authorisation in the EU. But there are still national and regional aspects to the authorisation, such as ethics committees. The Clinical Trials Regulation also introduces new requirements. It should be closely monitored whether the organisation and conduct of international trials have become less cumbersome and whether they support the needs of academia.

Reimbursement

- Reimbursement bodies need to put accessible and effective reimbursement procedures in place.
- New HTA methods and payment procedures are needed to make it possible for academics to have a role in personalised medicine with fair-priced therapies.
- Ideally, reimbursement, or at least HTA procedures, would be harmonised across Europe.

The upcoming revision of the general pharmaceutical legislation may be an opportunity to take some of these recommendations on board.

CONTENTS

INTRODUCTION

There are many cancers of unmet medical need. For example, there is no standard post-remission therapy to prevent relapse of acute myeloid leukemia. Also, there is a lack of approved pharmaceuticals, mainly because of the inability to bypass the blood-brain barrier, to treat glioblastoma multiforme. In addition, less than half of patients diagnosed with mesothelioma survive the first year after diagnosis. Other cancers with low survival rates include metastatic non-small cell lung cancer and diffuse intrinsic pontine glioma, which primarily affects children.

Fortunately, innovative therapies may resolve some of these unmet medical needs. Advanced therapy medicinal products (ATMPs) which are medicines based on genes, tissues or cells, offer ground-breaking new opportunities by addressing the root cause of disease. Traditional pharmaceuticals typically target a single drug-target interaction and mechanism of action that can be easily bypassed by tumour cells, resulting in disease relapse. Whereas ATMPs are based on cells with highly complex, novel modes of action, which interact differently with the human body compared to pharmaceuticals. While enacting anti-tumour responses they also generate immunological memory, enabling a long-lasting therapeutic response. Clinical trials have shown that for patients whose cancer relapsed after multiple treatments, ATMP treatment helped to achieve remissions that lasted for years (1, 2, 3).

The standard pathway to bring these new therapies to the patient is through commercial development by the pharmaceutical industry. Yet, this model does not provide ATMPs for all unmet medical needs because not every innovative therapy is commercially viable. Academic development of ATMPs may be an alternative solution for those in need. However, this pathway is not yet in place.

Building on research spearheaded by members of the Association of European Cancer Leagues (ECL), the ECL Access to Medicines Task Force explored the role that academia could play in the development of innovative therapies. Based on a literature review and analysis of four case studies of academically developed ATMPs, the Task Force presents its view on 1) hurdles faced by researchers and recommendations on how academia/non-profit institutions can best contribute to the development of ATMPs and their access at a fair price, and 2) how EU policies can favour an academic development of innovative cancer medicines where commercial ones are lacking.

ATMPs: CURRENT SITUATION

EU regulatory framework

ATMPs are regulated as a separate class of medicinal products under Regulation (EC) No 1394/2007. ATMPs can be classified into four main types: gene-therapy medicinal product, somatic-cell therapy medicinal product, tissue-engineered products, and combined ATMP. For this paper, we will focus on gene-therapy medicinal product and somatic-cell therapy medicinal product.

Gene-therapy medicinal products transport recombinant nucleic acid to the nucleus of the cells of a patient; this is achieved by using a vehicle, also known as a vector, that can deliver the transgene of choice while achieving stable and significant transduction of the target cells (e.g. being able to cross the blood-brain barrier) without relevant pathogenicity or immunogenicity (4). Gene-therapy medicinal products include ex-vivo genetically modified cells such as CAR-T cell therapy and direct delivery of recombinant nucleic acids by vectors to the patient (*in-vivo*).

In the European Union, gene therapies are regulated as ATMPs (medicinal product). Yet, cell-based therapies can be regulated as ATMP (medicinal product) or as human tissue and cells under Directive 2004/23/EC, depending on their intended function or extent of manipulation. If cells are used for the same essential function in the recipient as in the donor, or if they are not being substantially manipulated, they fall under Directive 2004/23/EC, and are authorised for use by the national competent authorities. Allogeneic stem cell transplantation is an example of such a cell-based therapy. Such therapies are non-ATMPs and therefore are not within the scope of this paper.

If cells are not used for the same essential function in the recipient as in the donor or if they are being substantially manipulated, they are regulated as ATMP (medicinal product), and authorised by the European Medicines Agency (EMA). Currently, the overarching Directive 2001/83/EC for medicinal products and Directive 2004/23/EC are under revision.

Developments and main actors

In April 2021, a total of 2,073 cell therapies were in the global pipeline, while 1,358 trials were targeting cancer. The majority of these trials (60%) focused on haematological malignancies, with the other 40% of trials focused on solid tumours (5). This vast pipeline continues to raise hope for new therapies. Recently, several ATMPs developed by industry obtained marketing authorisation. As of October 2022, the European Medicines Agency (EMA) approved 14 ATMPs (11 gene therapies, 1 cell therapy medicinal product, 2 tissue-engineered products), of which 6 are oncology ATMPs (6). This shows that the number of ATMPs for cancer treatment that actually reach the patient is still quite small. To increase it, several solutions are needed.

The development of ATMPs and conventional medicines differ. Due to the lack of commercial viability, the pharmaceutical industry is not heavily involved in the ATMP field compared to conventional medicines. ATMPs are often considered high-risk products, aimed at small patient populations due to highly specific underlying molecular mechanisms or new modes of action to target rare diseases, have limited opportunity for Intellectual Property (IP) protection, or have complex manufacturing procedures that suit a point-of-care setting in clinical practice. Thus, the market and commercial development of ATMPs is not going to meet all unmet medical needs. Understandably, the industry is highly unlikely to invest in therapies that will not guarantee a sufficient return on investment, even if the therapies can potentially be very beneficial for some patients. Withdrawal of several authorised ATMPs has indeed occurred due to market failure, which underlines the question of commercial value of certain ATMPs (7). Another disadvantage of commercial development is the high price setting. Commercially developed ATMP treatments costs between €300,000 to more than €1,000,000, which lead to issues with reimbursement and market failure (8).

Worldwide, academic medical centres play an essential role in research and innovation around ATMPs for cancer, specifically in preclinical research and early-stage clinical trials. A lot of knowledge is in the hands of academic medical centres and other public institutions, such as blood banks (9). ATMPs can be of autologous origin (source material such as blood originates from the patient who receives the treatment) or of allogeneic origin (source material originates from a donor). Many of them originate from clinical practice due to the close proximity of clinical, scientific, technological expertise to the patient or donor, who provide blood or other cellular material to generate ATMPs. Products such as autologous cell therapy, which are very patient-specific and suitable for a point-of-care model (i.e. manufacturing and treatment under one roof) are less commercially viable and will take longer to be picked up by private parties for further development (9). Thus, academic developers play an important role in the development of ATMPs however, they face many hurdles related to manufacturing, development, authorisation and reimbursement.

Several other stakeholders play a major role in the research and development of ATMPs. One such group is the public funding agencies, as commercially developed ATMP leans heavily on public funding. According to the NGO Knowledge Ecology International, the US National Institutes of Health (the US medical research agency), invested more than 200 million dollars in CAR-T research and development between 1993 and 2017 (10). Funding from charities is also important as can be seen from the promising results of several projects (11, 12). The spending of such high amounts of public funding should result in accessible and affordable ATMPs for patients in need.

Need for alternative development trajectories

There are several trajectories available to bring new products to the patient in clinical practice. The commercial trajectory for development of ATMPs undertaken by industry is suited for large patient groups such as lung cancer patients, as those treatments will need to be taken to the market on a large scale. Only the pharmaceutical industry has the infrastructure to produce enough treatments and capacity for global market entry. However, even though such products fit the commercial trajectory, access and affordability are hindered by commercial incentives. Fair pricing is a challenge for commercially developed ATMPs.

Large public and charity investment in academic developments can de-risk product development and therefore facilitate fairer prices for commercially viable innovative therapies that originate from academia. If an academic institution out-licenses research results or products to a private company, the licensing agreement should contain clauses guaranteeing access and affordability, without barriers to niche development (9). This hybrid trajectory between public and private development can be realised by more and fairer public-private partnerships or licence agreements with clear agreements on IP rights, returns and responsibilities, as well as more valorisation of results through spin-off companies.

In addition, a non-commercial, academically driven pathway should be put in place. This is essential to meet current unmet medical needs of cancer patients. Non-commercially viable ATMPs include, but are not limited to, autologous treatments for small patient populations. Such trajectory should guarantee the safety, quality and efficacy of treatments reaching patients. Costs of therapies in these trajectories (€35.000 to €60.000) are much lower than commercially developed therapies (12). Yet, provisions and measures can be put in place to facilitate academic developments. However, there are still many challenges and hurdles that need to be addressed in order to bring these treatments to the patient via a non-commercial, academically driven trajectory. In this paper, we try to shed some light on the challenges and propose some solutions. The literature review makes it clear that there are challenges in four areas:

First, **manufacturing** of ATMPs is difficult. Upscaling, especially in ex-vivo autologous cell applications is a challenge (8). It is not easy to create a structure that complies fully with good manufacturing practice (GMP) within a standard hospital environment that has sufficient capacity for phase III trials or clinical practice. It is expensive and logistically challenging. There are hurdles with respect to the availability of personnel, knowledge, infrastructure, and materials. In addition, the facility must meet GMP standards in the short and long term. However, the development of semi- or fully automated manufacturing systems to produce ATMPs under controlled conditions, makes it easier for academic hospitals to create a GMP compliant infrastructure (13). Academic hospitals can try to deal with these challenges by creating new organisational structures, such as a not-for-profit manufacturing unit or collaboration between an academic platform and a contract manufacturing organisation (7, 9).

A second challenge is related to the **collection of evidence**. It is not easy to collect evidence on the long-term safety and benefits of ATMP (8). Evidence provided by academic research does not always meet the requirements of the authorities responsible for authorisation or reimbursement of ATMPs. This makes it difficult to obtain marketing authorisation and reimbursement. One way to overcome this is to acquire early scientific advice from the regulators. However, when requesting early scientific advice, researchers experience barriers such as limited knowledge of the regulatory framework and opportunities and procedures for scientific advice, fears of interference with the intended research, and a regulatory lag at government agencies (9). EMA has recognised this problem and has launched a pilot to assist academics. However, the pilot

is limited, and will take time before it delivers. Also, the requirements of regulatory bodies (EMA and national competent authorities) and payers are not aligned. For example, their expectations around comparators and endpoints of clinical trials may differ. Moreover, for academic centres it is challenging to organise large, multicentre, late-phase clinical trials required for authorisation and reimbursement. Academic trials often take a long time because of lengthy recruitment periods. Consequently, scientific progress, such as the arrival of checkpoint inhibitors, may render a trial obsolete. Finally, the budgets necessary to run large-scale clinical trials in an academic context as well as to cover the costs associated with the regulatory development path are lacking.

Third, acquiring **authorisation** from a regulatory body such as EMA is not easy. Despite recent efforts by the EMA to reach out to academics (e.g. allowing them to use the PRIME scheme), authorisation procedures are geared to the resources and capabilities of the industry and are not accessible to academics. Regulatory procedures itself are very expensive. In addition, the holder of a marketing authorisation has several post-marketing responsibilities. Being a marketing authorisation holder entails legal liability. Within the current context, these duties are almost impossible for an academic institution to fulfil. Thus, it is not clear whether academic centres are suitable as marketing authorisation holders.

The existing EU legislation allows for the provision of ATMPs without clinical trials and market authorisation via the Hospital Exemption (HE). This entails the use of ATMPs in exceptional circumstances of unmet need when no other treatment options are available. The HE is granted on a national level under national provisions. However, the HE is not implemented in a consistent way across Europe. Some countries impose much stricter provisions than others. Therefore, the number of HE holders differ between countries. In France, Germany, Italy, Poland, Spain and the Netherlands, there are currently several HE granted, but in Austria and Belgium, no HE was granted, nor applications received (14, 15).

Fourth, ATMPs introduce specific challenges for health technology assessment (HTA) and **reimbursement decisions**. Compared to other treatments, the acquisition costs are high. This can become a threat to the affordability of health care systems (8). In this context, the lower prices of academically developed ATMPs (15) may be a trump card, if academics are able to convince payers and HTA bodies of the safety and added clinical benefit of their treatments.

LEARNING FROM EXPERIENCE - CASE STUDIES

To further explore the challenges outlined above and to propose possible solutions, we analysed four case studies.

WIDEA and MESODEC trials

Interviewee: Prof. Dr. Zwi Berneman is Hematologist at the Antwerp University Hospital.

Product and current status

The team of Prof. Dr. Berneman is conducting research on dendritic cell vaccination, for example, in acute myeloid leukemia and malignant pleural mesothelioma.

The WIDEA trial is researching Wilms' tumour (WT1) antigen-targeted dendritic cell vaccination to prevent relapse in adult patients with acute myeloid leukemia. This is a multicentre randomised phase II trial with participation of eight Belgian hospitals (ClinicalTrials.gov Identifier: NCT01686334). The preliminary evidence shows that the treatment has effects: in the dendritic cell vaccination arm some patients have reacted.

Currently, there is no standard post-remission therapy to prevent relapse in acute myeloid leukemia. If clinical efficacy and low toxicity can be confirmed in the large-scale, controlled WIDEA clinical trial, which would be the first of its kind, WT1-targeted dendritic cell (DC) vaccination can become the new standard post-remission treatment for acute myeloid leukemia patients older than 65 years or for younger high-risk patients who are not considered candidates for hematopoietic stem cell transplantation in the short term.

Malignant pleural mesothelioma is a highly aggressive, and in almost all cases, fatal cancer that is closely associated with prior asbestos exposure. Despite some improvement over time, the prognosis of a patient diagnosed with malignant pleural mesothelioma remains dismal with a median overall survival of only 12-18 months from diagnosis. In the single arm phase I/II MESODEC trial (First-line immunotherapy using Wilms' tumor protein 1 (WT1)-targeted dendritic cell vaccinations for malignant pleural mesothelioma (ClinicalTrials.gov Identifier: NCT02649829), the feasibility and safety of WT1-targeted dendritic cell vaccination in malignant pleural mesothelioma patients is investigated as frontline treatment in conjunction with first line platinum/pemetrexed-based chemotherapy, as well as the clinical effects including survival and the induction of mesothelioma-specific

immune responses. Results show that it is feasible to manufacture WT1/DC vaccines, and that it is feasible to administer these vaccines in combination with platinum/pemetrexed based chemotherapy. In addition, WT1/DV vaccines proved to be safe. Preliminary overall survival was 35 months, which clearly exceeds the survival of 12-18 months that is reported in literature.

Perspectives and strategy for access in clinical practice

Discussions have taken place with specialists and consultants regarding a broad implementation and marketing authorisation of dendritic cell vaccination. There is no intention to apply for market authorisation at EMA. Costs/effort for academic hospitals are too high. The Belgian regulator informed that the request for HE is not opportune for the type of patient-specific product and patient population researchers are working with, since the per patient national procedure from submission to approval takes too long. In Belgium, there are stringent requirements attached to the HE and GMP implementation which most hospitals cannot provide.

For the reimbursement of dendritic cell vaccination, discussions with the responsible Ministry took place in 2017-2019. A system comparable to the reimbursement of stem cell transplantation was considered. In stem cell transplantation, there is nomenclature for gathering and freezing cells and preparing the donor. For cell vaccines, a comparable nomenclature can be defined. The estimated cost per patient is €25,000-€35,000. A reimbursement application was submitted but was rejected as no randomised clinical trial was conducted. Whereas another form of ATMP, commercial CAR-T cells, were granted reimbursement based on single arm studies.

Bottlenecks

- Research on dendritic cells is supported by private charities. Non-commercial funding for large, randomised phase II or III studies is inadequate. Funding from charities is not sufficient for large scale studies.
- A European clinical trial platform is not up and running yet to facilitate the inclusion of other participating centres. Having an international multicentre study would be a big organisational challenge.
- The legislation on ATMPs is changing and becoming stricter. The requirements to comply with GCP and GMP in general and specifically for ATMP are increasing the overall operational clinical trial costs. Meeting the GMP criteria is expensive. Reimbursement and research funding must take this into account.
- The regulators are not always interpreting the guidelines in the same way (e.g., about the category of therapy). It is not always fully clear whether a treatment is a gene therapy.
- There is a lack of legal counsel and resources that represent the interests of academia in consultation rounds of the government regarding regulation on ATMPs. Academia cannot afford the number of support staff that is available in the pharmaceutical industry.

Recommendations of the researcher

- In general, the domain of ATMPs cannot be left solely to the industry. This has been proven by several market withdrawals of ATMPs in recent years. ATMPs are often not profitable enough. There are good examples of cell therapies provided by hospitals and not by companies (e.g. hematopoietic stem cell transplantation).
- For the manufacturing of cell and gene therapy, a point-of-care approach should be taken. This means that hospitals produce their own ATMPs, starting from reagents provided by the companies. This makes hospitals less dependent on industry. The manufacturing will also be cheaper and faster. For the moment, the Antwerp University Hospital is producing its own CAR-T cells in a facility that is a common initiative of the University of Antwerp, the Antwerp University Hospital and the Province of Antwerp.
- The authorities should define areas of unmet medical need where cell and gene therapy can be a solution and where the pharmaceutical companies show no interest. In these areas the authorities should define a pathway to authorisation and reimbursement that is accessible to academia. This pathway could take inspiration from existing systems. In Belgium, for example, the preparation of blood products for transfusion is organised by the Red Cross, a not-for-profit organization; hematopoietic stem cell transplantation is completely organised by hospitals. It should be made clear which level of evidence is necessary for reimbursement: is a phase II trial sufficient or not? If it is not sufficient, then there should be funding for large scale studies, e.g. the EU's Horizon Europe programme.

ARI-0001

Interviewee: Dr. Manel Juan is Immunologist at the Hospital Clínic of Barcelona.

Product and current status

ARI-0001 is an autologous CAR-T cell therapy targeting CD19. Currently, ARI-0001 is approved to be manufactured under a HE license in Spain. Treatment of patients older than 25 years with relapsed or refractory (R/R) acute lymphoblastic leukemia is reimbursed by the Spanish national health care system. This academic product fulfils an unmet medical need. It is complementary to a commercial product that was granted marketing authorisation by EMA.

Trajectory

ARI-0001 is an autologous CAR-T cell therapy that is comprised of an anti-CD19 monoclonal antibody that was developed by the Hospital Clínic of Barcelona from 2011 onwards. This trajectory was initiated because the originator laboratory in the United States was taken over by industry, which made it difficult to produce an academic product for a few patients per year in their own hospital. It also took industry six years to make the CAR-T available, putting access for patients under pressure.

In 2017, an exploratory single-arm trial was initiated to evaluate ARI-0001 in acute lymphoblastic leukemia, chronic lymphocytic leukemia and non-Hodgkin's lymphoma (17). Spanish national competent authority considered evidence as most compelling in patients with acute lymphoblastic leukemia. Clinical outcomes continue to be measured and results show ARI-0001 has comparable outcomes to the commercial products. The initiated trial was based on the earlier developed antibody to treat patients outside commercial labels. ARI-0001 was not transferred to industry to ensure that the product would not be shelved. The trial was funded by the health authority of Catalunya and additional funds were raised by a private non-profit foundation through crowd funding. A subsequent trial was initiated to collect more evidence. This was reported to the national competent authority which has been very supportive throughout the whole process. This support has been critical and enabled learning from both sides.

Perspectives and strategy for access in clinical practice

There is a role for academia in the development of therapies for rare and paediatric disorders or diseases. In the future, treatments will be designed for a specific target for few patients. The traditional route is through industry, but niche products for few patients have no commercial value or are put on the market for high prices. Still academia and industry can co-exist. Industry can reach a very wide, global scale of product availability.

The Hospital Clínic of Barcelona wants to make ARI-0001 available for other centres too, although the primary aim was to make it available for their patients in the hospital. For Spanish national competent authority, it was important to engage with the EMA. In consultation with the EMA, the hospital applied for a PRIME designation, as a first step towards a centralised marketing authorisation that would enable market access in the European Union. ARI-0001 was granted PRIME designation after a regulatory process of one year. The EMA now invited the hospital to apply for a centralised marketing authorisation, as part of a pilot to offer enhanced support to academic and non-profit developers of advanced therapy medicinal products.

Bottlenecks

- Long duration of regulatory and health technology procedures. Difficulties to understand regulators and vice versa, pharmaceutical regulations that do not fit cell and gene therapies very well. Long assessment durations cause delay.
- Long trial duration. The trial took five years to complete. Most difficult aspects to complete the trial were to collect the appropriate preclinical data, which had poor value to predict clinical outcomes, plus the time and funding that was needed. Compliance was reached by following regulations and by using costly methods for safety data such as CAR reactivity.
- Personnel capacity to compile a dossier for centralised marketing authorisation, with regard to the documentation that is required.
- Regulations are geared towards industry and make it difficult for a hospital to be a license holder. For instance, the Manufacturing/Importers Authorization mandates that only companies can export to other Member States.
- Reimbursement for rare and paediatric disorders or diseases, including when medicinal products are re-purposed. The process to gain reimbursement here was lengthy (4 months).

Recommendations of the researcher

- For academics to play their role in development of rare and personalised medicines, regulations for complex products such as cell and gene therapies will need to become more flexible, specifically in the early stages of product development (e.g. phase I trials). For example, small modifications to the manufacturing protocol to optimise treatment and/or safety during a trial is not allowed.
- It can be questioned whether the right regulatory framework is used. The rules and the concepts for cells are similar to pharmaceuticals, but the rules for transplantation are more apt as CAR-T's are made from autologous cells.
- Patients should come first. If the incentive is better care for the patient, instead of profit, it is justified to have more regulatory flexibility for academic hospitals compared to industry if that regulatory flexibility benefits the patient.
- Need for a European regulatory framework that is applicable in all Member States for all aspects of medicinal product development and marketing. In interactions with regulators for new innovations it would be helpful to meet regulators that have broad instead of specific knowledge.
- The system for regulatory fees and specific fees for academics can be improved. Funding could partially come from government funds or taxes, similar to the system in the United States.
- New reimbursement methods are needed that would allow academics to play their role in rare and personalised medicine.
- There is a need or desire to collaborate more among academics, to form networks among centres so knowledge can be shared.

Tumour Infiltrating Lymphocytes

Interviewee: Dr. Inge Jedema is Head of Translational Cellular Therapy at the Netherlands Cancer Institute (Antoni van Leeuwenhoekziekenhuis) in Amsterdam.

Product and current status

Tumor Infiltrating Lymphocytes (TIL) is an autologous therapy developed by the Netherlands Cancer Institute (NCI). The TIL is a tailor-made fresh product, without cryopreservation, and manufactured in a point-of-care setting. The therapy is developed for patients with relapsed or refractory advanced melanoma after immunotherapy. Even though immunotherapy has been an enormous improvement, still many patients relapse. For these patients there is a clear need for more therapeutic options. A randomised phase III trial was finalised in 2022, outcomes were recently published (18) and presented at the European Society for Medical Oncology. Results show that the median progression-free survival was significantly higher in the TIL group compared to the ipilimumab group (7,2 months vs. 3,1 months, resp.) The objective response rate was 49% of patients in the TIL group, versus 21% of patients in the ipilimumab group. The Dutch National Health Care Institute recently released a positive Health Technology Assessment (HTA) outcome, the TIL therapy will be reimbursed from 2023. The NCI is preparing for a centralised procedure for marketing authorisation at the EMA.

Trajectory

The concept of TIL therapy was brought to the Netherlands by the NCI in 2008, from the originator laboratory in the United States. A European GMP-compliant manufacturing process was developed, after which an exploratory trial was initiated. In 2014, a randomised phase III was initiated, in which TIL therapy was compared to treatment with the checkpoint inhibitor ipilimumab. In total, 168 patients were enrolled at two sites: the NCI and the Center for Cancer Immune Therapy (CCIT) in Copenhagen, Denmark. To ensure sufficient production capacity for the Netherlands, the Laboratory for Cell therapy of Sanquin Bloodbank produces the TIL therapy together with the BioTherapeutics Unit of the NCI for Dutch patients.

The phase III trial was funded through the initiative ‘conditional reimbursement’ of the Dutch National Health Care Institute, meaning treatment costs of the phase III trial were reimbursed from the Dutch basic health care insurance (19). Continued public funding by the Dutch National Health Care Institute, ZonMw and KWF Dutch Cancer Society have been key to finalise the trial, also during more difficult times.

Perspectives and strategy for access in clinical practice

The NCI wants to make this therapy available at a fair price to ensure treatment. Therefore, a clear role for academia is foreseen to bring the TIL to clinical practice. The TIL development has exclusively been conducted by academia, with public funding. No companies have been involved so far. The NCI now aims for EU marketing authorisation because of two reasons. First, a Dutch HE would become invalid once similar centrally authorised products would become available, including commercial products from other regions such as the US. EU public investment and treatment availability at a fair price would be lost. Second, the NCI wants to make the treatment available in the Netherlands first, and work with licenses and technology transfers to other European centres to expand availability in Europe. With a European marketing authorisation and manufacturing process, most problems would be solved to make it available in other EU countries. To do technology transfers for production in other 'centres of excellence' would be most challenging and require a lot of training. Centralised training locations to deliver the required knowledge for a particular country is considered as a solution. They can attempt to reach EU marketing authorisation with funding from KWF Dutch Cancer Society.

Bottlenecks

- National clinical trial approval procedures. When the phase III trial was initiated in 2014, the Clinical Trials Regulation (Regulation (EU) No 536/2014) had not been in place yet. The NCI wanted to include multiple clinical sites in multiple European countries. Yet, the regulatory differences among countries, and the interpretation of the data and requirements were different among competent authorities. The trial was evaluated as new in each country, and a completely different protocol from the one that was approved in the Netherlands was requested. This caused delay to finalise the trial and impeded a timely design upon finalisation.
- Entering a procedure for centralised marketing authorisation. Capacity and regulatory knowledge for centralised marketing authorisation is limited in academia.
- Bringing and maintaining a product on the market as academia is challenging. An entity needs to be license holder and hold responsibilities for the product. The responsibilities would be difficult to handle for the NCI. Data systems are needed to handle all production sites and treatment. Data exchange would be challenging. An alternative could be point-of-care production sites that are overseen by a separate new entity. Out licensing is not desired, because the production process requires close proximity between production and treatment. All knowledge would need to be transferred as well.
- Manufacturing and quality control of a fresh, living, tailored-made product. The TIL is not cryopreserved, meaning all assays for quality control need to occur before release of the product. Assays for release are challenging, yet efforts are made to develop a potency assay. The TIL product is also not identical between patients. TIL consists of different T-cells and their respective receptors, based on the T-cell population of the patient. The tumours are also heterogenous, by modifying the product you would introduce a bias. Harmonisation between production sites and how to test comparability among sites and patients is very challenging with a TIL therapy.

Recommendations of the researcher

- An academic registration trajectory to overcome challenges for ATMPs developed by academia.
    - Support with all procedures and requirements to ensure efficiency when a new group aims for EMA submission, without lowering requirements for an approval. Fees can be lowered if you are not a commercial entity. Schemes such as PRIME could offer a solution.
- Modifications to the HE.
    - More protection of national HE licenses would be a possibility to protect academic products and treatment within a hospital. Yet, this could create an unlevel playing field. This would need to be solved or mitigated to become a feasible solution. An academic registration trajectory is preferred.
- Regulatory flexibility: a shift from product regulation to process regulation in relation to clinical outcomes.
    - The TIL is considered to fit in medicinal product regulation, because of the risks involved and the extensive in-vitro manipulation. Yet, it needs to be discussed which manufacturing and quality exemptions can be made for products like the TIL that do not fit current regulations very well. It should be possible to analyse and verify that clinical outcomes are comparable among production sites with tailored-made products.
    - To determine which exemptions can be made for certain ATMP subtypes, and which requirements need to be in place, it is important to distinguish between vivid and non-vivid products (such as vectors). For vivid products dosing is difficult, they will proliferate when you administer them. They are personalised, so all autologous and vivid products are a different set of products. Cryopreservation gives you time, for testing, for distribution, which is not available for the TIL.
- Flexibility from HTA bodies and funding schemes similar to the 'conditional reimbursement' in other European countries to fund late-stage trials.
- Ideally HTA decision-making could be harmonised, yet it would be very difficult to arrange reimbursements on a European level. This would require defining taxation policy at the European level as well.

Heidelberg - manufacturing of CAR T

Interviewee: Prof. Dr. Stefan Eichmuller, Head of Research Group GMP & T Cell Therapy, German Cancer Research Center (DKFZ), Heidelberg, Germany.

Product and current status

The research group is doing research on TCR (transgenic t cells), artificial t cell receptors, CAR T. In a collaborative project they are presently establishing new GMP facilities to produce cell-based immunotherapies, such as CAR T cells.

Perspectives and strategy for access in clinical practice

A purely academic development trajectory is feasible for very individualised cell therapy for small groups of patients, e.g., individual T cell receptors. A pharmaceutical company will never be interested in individualised treatments for small groups of patients, such as artificial T cell receptors. Therefore, academic hospitals play an important role but they need funding. As acquisition costs of commercially available CAR T are quite high, it makes sense to set up a local not-for-profit production capacity for CAR T cells. The analysis shows that the cost per product would be between €45.000 and €60.000 (16), depending on the system used for gene transfer, the number of machines per clean room and in case of maximal utilisation.

In addition, the current centralised production process raises questions about the impact on quality. In the current system, it can take months before the therapy can be administered. Cells have to be taken from the patient, frozen, then shipped to a laboratory where they are manipulated, frozen again and shipped back to the clinic. Freezing leads to quality loss (13). Technological developments such as closed manufacturing systems makes this more feasible.

If hospitals were to build clean rooms, companies could also make contracts for the use of their viral CAR vectors. The CAR construct of the company could be used to modify the T cells of the patient in these clean rooms. Maybe they would make less money per treatment, but there may be other advantages such as having a better-quality produce and being able to treat more patients.

Bottlenecks

- The establishment of GMP facilities is a time-consuming process. The organisation is underestimated: staff is needed to deal with the necessary permissions, to get resources to produce the product, physicians who are willing to apply it, someone who is going to write trial applications etc. Once a clean room is in place, it still can take years before treatments for patients can be produced.

- For academic groups, it is very difficult to set up a complete development trajectory from the preclinical phase to phase III due to the expense. There are no available budgets, and NGO's such as The German Cancer Aid cannot finance phase III trials.
- Authorities do not make it easy in early phases of clinical research on personalised treatments. There are strict requirements to use experimental therapies, which slow down the process. Some of the questions one must answer before the trial can only be answered with information collected by the trial (e.g., proof of potency). Requirements and demands of authorities in early phase trials should be reconsidered.
- Contributing to international phase III trials is not easy. The team wanted to participate in the Dutch TIL-trial. Also, academic groups in Denmark and Spain were approached. In Germany, the team had to go through the complete regulatory approval process again. The German authorities did not consider that the Dutch authorities agreed with the trial. They had to install extra control systems in accordance with national legislation. This took a lot of time and in the end, they were not able to participate. It remains to be seen whether the Clinical Trials Regulation will solve all the issues.
- For the very individualised therapies it is not clear how the authorisation after the research phase should be organised. There should be permission to apply a concept or procedure. It is difficult to give an authorisation for a product because the product is different in every single case.

Recommendations of the researcher

- To make the process of acquiring a GMP accreditation easier, national and European authorities should adjust the rules according to technological developments e.g., closed systems to produce cell therapy. The demands of the clean room should not be as strict if CAR T production is done in a closed system.
- European and national authorities should simplify the permission for research on cell and gene therapies. The Food and Drug Administration (FDA) in the USA is a good example: FDA has discussions with researchers on new developments and how they can be embedded in the legislation.
- The organisation of approval process for international trials at European level or at least harmonisation of rules across all European countries could speed up the process for multi-national trials.

CONCLUSIONS

ATMP is an area in which academic, non-commercial development plays a vital role. The four case studies show the efforts made by academics to improve the fate of patients with limited or no further treatment options. They are developing cell and gene therapies for subgroups of patients without access to marketed products, or tailor-made personalised treatment, with complicated manufacturing procedures in a point-of-care setting. These developments are crucial for patient groups with needs in which the industry is not interested due to commercial reasons.

The European authorities are aware of academic ATMP development. To support that, EMA launched a pilot which we fully endorse. Five ATMP developers targeting unmet clinical needs will receive dedicated assistance which include guidance and fee reductions and waivers. The aim of this pilot is to assess the level of regulatory support needed to boost the number of ATMPs that reach patients.

The bottlenecks that we identified in the case studies include regulatory hurdles, but also stem from limited funding and lack of collaboration opportunities.

In a nutshell:

- Regulations are geared towards industry and hinder European access to academic products. For academic hospitals, it is impossible to make treatments available in other Member States. Export of licensed products is restricted to companies, and export of HE products is not allowed. The HE can be a temporary solution for national access, but national schemes differ to a large extent. This hampers international collaboration and European access.
- The entity holding the market authorisation has liability and post-marketing responsibilities and obligations, such as pharmacovigilance procedures. It is difficult for an academic entity to handle these responsibilities.
- For academics, it is difficult to understand which regulatory framework is applicable and suitable: for some cell therapies, the legislation about transplantation seems more fit for purpose than the regulations about medicinal products.
- Research in the early clinical phases of the R&D trajectory is often confronted with very strict requirements and demands in relation to manufacturing and quality. It is very challenging to meet these requirements in early clinical development, in particular with highly innovative products. Required evidence for trial approval may only be available after the collection of data during the trial, such as proof of potency.
- Creating a fully compliant GMP structure for the manufacturing of ATMPs within a standard hospital environment is expensive and logistically challenging.
- For academic groups, it is very difficult to set up a complete development trajectory from the preclinical phase to phase III. One main reason is difficulty in the securing budgets for the phase III trials.
- Organising large multinational clinical studies has been difficult due to regulatory differences for clinical trial approval among countries. The new Clinical Trials Regulation may offer solutions, yet the outcomes of its implementation are still unknown.

- In later stages of development, it may also be very challenging to meet manufacturing and quality requirements that mandate quality control for the end product instead of standardised procedures, with a fresh, living, tailored-made products that differs from patient to patient. The authorisation and requirement regulatory framework for personalised treatments is not yet clear.
- Entering a market authorisation procedure and other regulatory procedures is expensive and lengthy.
- Standard reimbursement procedures are not fit for purpose for treatments for rare and paediatric disorders or diseases.

ATMPs have the potential to tackle high unmet needs in cancer treatment. Developing and making these products available cannot be fully left to the pharmaceutical industry. The industry will naturally focus on commercially viable product, and therefore will not solve every unmet need. This provides a clear role for academia, specifically when it comes to the development of niche personalised treatments and therapies for rare, paediatric disorders or diseases. If the above-mentioned challenges are overcome, we foresee a complementary division of labour. On one hand, industry would focus on the development and large-scale production of ATMPs for large patient groups. On the other hand, academic hospitals would develop small scale production of personalised treatments, under a point-of-care manufacturing and administering model (9, 13).

RECOMMENDATIONS

We put forward the following recommendations to support academic development and to bring treatments to patients quicker:

Regulatory framework

- **There is a need for a non-commercial academic pathway to the patient, leading to an authorisation by the EMA. This is important to make ATMPs available to patient groups with high unmet needs.** This includes an academic registration trajectory, with lower or no regulatory fees; some regulatory flexibility to take the very small patient populations and the intricate complexity of niche and personalised treatments into account, support to academics to fulfil the procedures and requirements. This process should lead to treatments that **are as qualitative, safe and effective as treatments** sprouting from the traditional commercial pathway. We highly encourage the development of the current EMA pilot for ATMP development further into a formal pathway.
- Limitations to implement a new ATMP in clinical practice by academia need to be alleviated to **ensure access across the EU**. Fees for marketing authorisation and reimbursement procedures need to be lowered or waived for academia. Academic authorisation licenses should be valid in all EU Member States without export issues.
- For personalised treatments or niche ATMPs for ultra-rare diseases and other exemption situations, the Hospital Exemption (HE) remains necessary. However, because there are countries which use it in different ways, there is need for some harmonisation of the adoption at a centralised level of some operational criteria that have proven to work at the national level (13). **The treatment under HE should be accessible for every European patient in need of the product**. Data should be collected to monitor outcomes, but not necessarily to build a dossier for marketing authorisation, as niche products are likely to fail in a commercial setting or meet the needs of only a few patients. An unlevel playing field can be avoided by using the commercial marketing authorisation pathway, the non-commercial academic authorisation pathway, and the HE in a complementary fashion. They should be parallel to each other without overlap, for the purposes of commercial development, non-commercial development, and exemption situations, respectively. Current HE licenses that exceed exemption situations should be offered a transition period to obtain an EMA authorisation. These adaptations to the HE would only benefit access if a non-commercial academic pathway is realised.
- European and national authorities should take the specificities of early phase research into account when authorising clinical trials. **Discussions between researchers and regulators** on new developments and how to embed them in the legislation can be very useful. These dialogues are also relevant to adjust the regulatory system to new technological developments, such as closed manufacturing systems and a shift from product regulation to process regulation in relation to clinical outcomes.

Funding

- Funding bodies, HTA bodies, and health insurance funds should ensure that public funding for late phase clinical trials and regulatory procedures is available for breakthrough ATMPs developed by academia.

Collaboration

- Collaboration among academic hospitals should be stimulated, so that knowledge on topics such as good manufacturing practice (GMP) and quality control, and GMP manufacturing capacity, may be shared. These **academic networks** are also vital in making treatments available across Europe and in setting up international clinical trials.
- The Clinical Trials Regulation facilitates a harmonised and more efficient system for clinical trial authorisation in the EU. But there are still national and regional aspects to the authorisation, such as ethics committees. The Clinical Trials Regulation also introduces new requirements. It should be closely monitored whether the organisation and conduct of international trials have become less cumbersome and whether they support the needs of academia.

Reimbursement

- Reimbursement bodies need to put accessible and effective reimbursement procedures in place.
- New HTA methods and payment procedures are needed to make it possible for academics to have a role in personalised medicine with fair-priced therapies.
- Ideally, reimbursement, or at least HTA procedures, would be harmonised across Europe.

The upcoming revision of the general pharmaceutical legislation may be an opportunity to take some of these recommendations on board.

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