Increasing Patient Access to Advanced Therapies; the UK Perspective

Over the past five years, we have seen remarkable growth and clinical results in an area of medicine known as advanced therapy medicinal products (ATMPs), which comprise gene therapies, somatic cell therapies, and tissue engineered products. These treatments offer the potential to address significant and growing unmet healthcare needs. They offer the promise of treating and altering the course of diseases which cannot be addressed adequately by existing pharmaceuticals, offering a lifeline to some patients who have failed all other treatment options.

The field of advanced therapies is relatively new, however advances in technology have driven this industry to grow at a significant rate both in the number of clinical trials being run, and companies developing products. At the time of writing, there are nearly 1000 companies worldwide, with over 230 companies headquartered within Europe[1]. Consequently, the number of clinical trials has grown at pace, a worldwide increase of 32% from 2014–2019, with over 2000 trials initiated in this period and 323 centred in Europe. There are also 129 multi-regional trials, most likely including at least one European country[2]. The expanding activity is reflected in the UK accounts with 127 ongoing trials; 12% of all global clinical trials in this field. Oncology has been the dominant therapeutic area for a number of years, blood cancers in particular; however, there are trials examining a broad variety of indications, with oncology now being just 39% of trials (Figure 1.)[3].

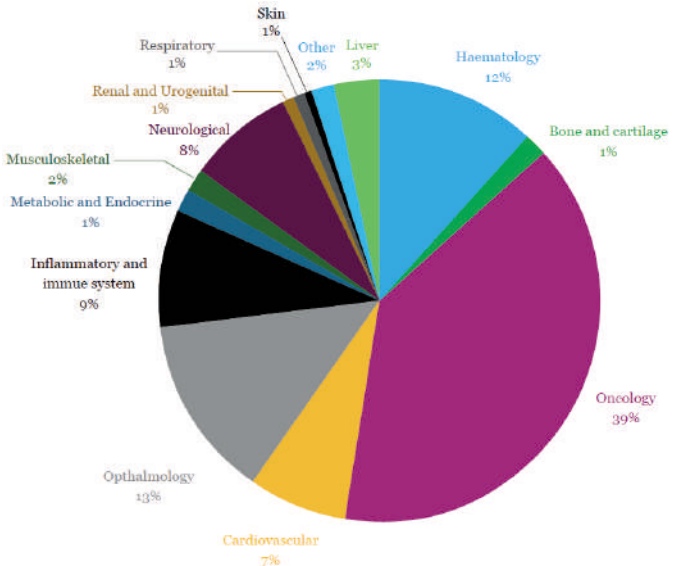

Figure 1: Distribution of UK ATMP clinical trials according to therapeutic area in 2019

Whilst there are advantages for patients coming from these newer therapies, they pose many challenges to healthcare systems around the world. Currently, most of the cell therapy treatments in development are autologous, meaning the product is manufactured from the patient's own cells. The cells are transported to the site of manufacture and, following release, the product is shipped to the hospital for patient treatment. The orchestration of this complex supply chain requires hospitals to adapt their infrastructure and this will be increasingly so as more of these products become available.

The UK is committed to providing patients with access to these novel treatments and was one of the first countries to approve the use of one type of ATMP in the healthcare system – Kymriah™ and Yescarta™ CAR-T therapies (chimeric antigen receptor T cell therapy) directed against the tumour antigen CD19. These two treatments were approved for use within the NHS in England through the Cancer Drugs Fund soon after receiving their EU marketing authorisation.

Another confirmation of the UK Government's support to the sector of advanced therapies was the investment in the Advanced Therapy Treatment Centre (ATTC) network programme; a network of centres designed to develop systems and processes to support the routine supply and delivery of advanced therapies by the NHS. The ATTC Network Programme is a world-first. Three Advanced Therapy Treatment Centres spanning the UK operate within the NHS framework, coordinated by the Cell and Gene Therapy Catapult, to address the unique and complex challenges of bringing pioneering ATMPs to patients (Figure 2). The three centres in the network are:

- Innovate Manchester Advanced Therapy Centre Hub (**iMATCH**)
- Midlands-Wales Advanced Therapy Treatment Centre (**MW-ATTC**, comprising Birmingham, Bristol, Cardiff, Leicester, Nottingham and Swansea)
- Northern Alliance Advanced Therapies Treatment Centre (**NA-ATTC**, comprising Edinburgh, Glasgow, Leeds and Newcastle)

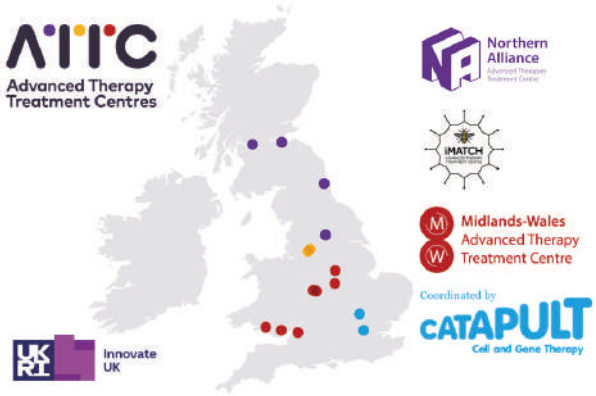

Figure 2: The UK network of Advanced Therapy Treatment Centres

The network, funded by the Industrial Challenge Strategy Fund, has the aim of building the skills and experience across the network as well as creating easily run and ready-to-use systems and solutions that can be rolled out more widely across the NHS in the United Kingdom.

The Cell and Gene Therapy Catapult has the core purpose of building a world-leading cell and gene therapy ecosystem in the UK as a key part of a global industry, and supporting the ATTC network is a significant activity in delivery of this ambition.

Some of the key activities of the ATTC network are described below.

Pharmacy
Pharmacists are responsible for the supply of licensed medicinal products, ensuring that the ordering, storage, reconstitution and dispensing of ATMPs are in line with their product specifications. The national Pharmacy Working Group (PWG) is acting as an expert and informed body to support the activities of the three ATTCs in the optimisation of administration of ATMPs. The group consists of pharmacists from across the UK that specialise in the governance, clinical trials, prescribing, administration and monitoring of ATMPs, and is an excellent example of collaboration across the NHS. The aims of the group are to promote good practice, and identify and resolve pharmacy issues to maximise the effectiveness and development of services for hospitals to administer advanced therapies. The group is developing a series of guidelines and checklists in the handling of ATMPs to provide consistency in pharmacies across the country.

Training
A highly-skilled workforce is key to the successful adoption of ATMPs into mainstream clinical practice. Experienced professionals from within the ATTC network are creating a combination of educational resources that will equip the NHS with the knowledge they need to be able to carry out their roles effectively when treating patients with advanced therapies. The training will consist of a series of e-learning modules that will cover basic introductory training to ATMPs, through to a detailed knowledge of the products, their applications, their side-effects and their manufacture, supply, delivery and follow-up. This initiative is, overall, preparing the UK healthcare workforce for the introduction of novel treatments across the NHS, providing access to high-quality educational material. The result is that all staff will be able to fulfil their roles effectively and understand how they facilitate the treatment of patients with these therapies.

Supply Chain
The performance of the supply chain for these living therapies is key to the safe and effective treatment of patients. The ATTCs are working with supply chain specialists to track and trace both the patient's starting material going from the hospital to the therapy manufacturing facility and the medicine returning from the site of manufacture back to the patient. We are also working with logistics operators and hospitals to be able to effectively coordinate the transportation of ATMPs. The electronic capture of the data and tracking of the cells throughout their journey is crucial to ensure the patients' safety at point of delivery. Supporting the creation of teams that effectively collaborate to deliver these treatments is a key, as many of these treatments are time-critical and success relies on an integrated and transparent supply chain, keeping everyone fully informed so they may schedule their activities to deliver the best patient care.

Standardisation of Starting Material for Use in the Manufacture of ATMPs
As demand for access to new ATMPs increases, driven by the growing number of clinical trials and/or by commissioned services, it is essential to identify and address potential bottlenecks in the supply chain. One such bottleneck that could arise, unique to ATMPs as a class of medicines, is the capacity within the healthcare system to 'procure' starting material from an increasing number of patients. Cell and tissue procurement is time-consuming and requires specialist staff and equipment. Furthermore, each ATMP has its own specific procurement requirements and the impact of limited space and limited safe cryopreservation technologies on large-scale storage will most likely be felt as the implementation of these treatments grows. The ATTC has a project, SAMPLE (Standard Approach to atMP tissue colLEction), examining the standardisation of the collection, preparation, labelling and transport of starting materials, e.g. apheresis, solid tumour material. The project brings together NHS, developers and equipment providers.

Within the SAMPLE project, the ATTC network aims to reduce unnecessary complexity and variation in apheresis collection. The network is also examining critical quality attributes of apheresis cryopreservation protocols to produce an optimal ATMP starting material for ATMP developers.

For surgical tissue, an aseptic fresh-frozen process suitable for ATMP manufacture is being developed. Expertise from developers, equipment suppliers, UK blood services, tissue banks, clinical teams and biobanks is being gathered to ensure quality and safety of tissue procurement in a robust, efficient and compliant manner.

Patient Involvement and Engagement
ATMPs are significantly different from conventional medicines and some of the key differences can impact both patients and their families. Notably for some advanced therapies, this can include 'curative' potential, possible side-effects, and use of the patient's own tissues and cells. Ensuring patients understand both the benefits and risks associated with developing and delivering ATMPs is imperative.

Knowledge Sharing
In preparation for an increased number of ATMP products being adopted into clinical practice, sharing knowledge across the ATTC network has been identified as a key strategic activity. A crucial part of this project as a whole is to effectively create and share expertise across the network, as well as more widely across the UK. Linking in with hospitals that have not run ATMP trials and supporting their development of the infrastructure and implementation of the changes required allows the wider NHS to bring these medicines to patients.

Using Technology to Record Patient-reported Outcomes for ATMP Patients
Part of the assessment of the value of ATMPs by NICE (National Institute for Health and Care Excellence) in the UK is to assess the impact of these new therapies. There is a need to demonstrate that these products are effective over the long term. A single administration of an ATMP improves a patient's health over a period of years; however, there is a need to provide a means of gaining an insight into the way patients perceive their health

and the impact that treatments have on their quality of life. This assessment needs to occur both at the point of receiving therapy and over long-term follow up once the patient has been discharged. It can be difficult to monitor patients once they have returned home and stop seeing medical teams on a regular basis.

The PROmics™ (Patient-Reported Outcomes assessment to support accelerated access to advanced cell and gene therapies) project is developing a device to allow real-time identification of side-effects following therapy and how it has impacted on patients' quality of life. This should facilitate clinical intervention and ensure patient safety in the adoption of advanced therapies within the NHS. Patients will be able to report how they feel on the treatment by using electronic devices. This data will also be used to assess the effectiveness of the treatment and be used as an evidence base for regulators and policy-makers to make informed decisions to support uptake in the NHS. Patients have been directly involved in development of the project and will provide direct input into the system development to ensure that it meets their needs.

Industry Advisory Group

It is important that the systems developed by the ATTCs meet the needs of the NHS, as well as those of industry. The ATTC Industry Advisory Group (IAG) was established to bring ATMP developers and supporting industry together to address key challenges they have in common and advise on the ATTC programme. The core focus of the group is to enable early traction of new advanced therapies by engagement with ATTCs and developing standards and best practices across the industry in the UK and internationally. Recently, the group has been joined by representatives from NHS England to ensure alignment for clinical adoption.

Conclusions

The approval of two CAR-T therapies and the press coverage these have received has shone a light on ATMPs and significantly raised their profile, both in the industry and the population as a whole. This raises the expectation that patients will be able to access these treatments easily. Currently, across the UK, some NHS hospitals are successfully delivering ATMPs to patients, but these are currently in small numbers for commissioned treatments or as part of clinical trials. There is an expectation of significant increase in patient numbers due to the anticipated number of trials and approvals of ATMPs. The Accelerated Access Collaborative (AAC) has undertaken a horizon scan of ATMP developments and conclude there are 30 ATMPs expected to undergo NICE assessment in the next three years[4].

Whilst the EMA and payers may approve the medicines for use in a national healthcare setting, this doesn't immediately translate into easy patient access. By funding the Advanced Therapy Treatment Centres, the UK government has set itself apart from other countries to provide a coordinated approach nationally to adopting ATMPs in the most straightforward manner possible. Other activities, such as the formation of the AAC, see a collaboration of multiple stakeholders feed into the advancement of new innovations such as ATMPs into the clinic[5]. Reaffirmation that advanced therapies are a key element of the UK life science strategy is also welcome[6].

As the industry around advanced therapies grows and matures further, the UK is positioning itself to be well placed to support the adoption of these treatments into the clinic; through a well-prepared clinical research network, hospitals with the infrastructure to deliver them and a workforce that is educated and skilled in their delivery.

INDUSTRIAL STRATEGY

UK Research and Innovation

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REFERENCES

1. Alliance for Regenerative Medicine Q3 2019 Quarterly Regenerative Medicine Sector Report; http://alliancerm.org/wp-content/uploads/2019/11/ARM_Q3_2019_FINAL-1.pdf
2. Alliance for regenerative medicine, Clinical trials in Europe 2019; https://alliancerm.org/wp-content/uploads/2019/10/Trends-in-Clinical-Trials-2019-Final_Digital.pdf
3. Cell and Gene Therapy Catapult, UK clinical trials database 2019; https://ct.catapult.org.uk/resources/cell-and-gene-therapy-catapult-uk-clinical-trials-database
4. https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/01/aac005-atmps.pdf
5. https://www.england.nhs.uk/aac/what-we-do/what-innovations-do-we-support/
6. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/857348/Life_sciences_industrial_strategy_update.pdf

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