Review

Bringing Advanced Therapy Medicinal Products (ATMPs) for Parkinson’s Disease to the Clinic: The Investigator’s Perspective

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Abstract. There is much excitement around the use of advanced therapy medicinal products (ATMPs), including cell and gene treatments, in Parkinson’s disease (PD). However, taking an ATMP to clinical trials in patients with PD is complex. As such it is important from an investigator’s perspective that they ask themselves two key questions before embarking on such work: firstly, why are you doing it, and, secondly, do you understand what is needed to conduct a clinical trial with that product. In this article, we briefly discuss these two questions.

Keywords: Parkinson’s disease, ATMP, stem cells, gene therapy, clinical trial, regulations

INTRODUCTION

Advanced therapy medicinal products (ATMPs) include tissue engineered products as well as cell and gene treatments, and there is much excitement around treating Parkinson’s disease (PD) with such therapies. These treatments need to be seen as distinct from advanced therapies for PD, such as deep brain stimulation or infusional dopamine therapies. Furthermore, it is critically important at the outset of this short review to distinguish between those therapies that have been developed over many years from sound scientific principles from those that have little or no scientific basis. One particular area of concern, in this regard, is the burgeoning field of stem cell tourism with clinics offering unproven stem cell therapies for money and for which physicians have a duty of care to warn patients about them when approached or asked [1–3].

In PD, the majority of ATMPs that are in, or soon to enter, the clinic are designed around replacing or restoring dopaminergic innervation in the striatum [4]. These approaches can simplistically be thought of in terms of:

- cell replacement therapies using stem cell derived dopaminergic neurons that are then grafted to the striatum;
- dopamine gene therapies that are designed to transfected resident cells within the striatum to facilitate the production of dopamine that can then be released locally at this site; and,
- neurorestorative approaches that use typically either gene therapies encoding for growth factors (e.g., AAV2-neurturin) [5] or cell therapies
that release a range of possible growth factors (e.g., the Spheramine® cell therapy) [6].

The rationale for the first two therapies is to directly replace the striatal dopamine loss of PD while, for growth factors, it is to rescue or slow down the loss of the failing dopaminergic nigrostriatal pathway. In all cases, the therapies are not designed to be curative as none are targeting the fundamental problems that lead to, and drive, PD. Rather, what they are seeking to do is to provide better symptomatic control of the dopaminergic responsive elements of the patients’ disease. These elements, which include rigidity, bradykinesia as well as the tremor and cognitive deficits in some PD patients, are not inconsequential to the quality of life and symptomatic control of their condition, as is evident by the power of oral dopamine drugs to dramatically help these aspects of PD [7, 8]. Thus, ultimately the best that these therapies can hope to achieve is to obviate the need for any oral or enteral dopaminergic therapies and the complications that these treatments bring with them [9]. As such ATMP therapies could dramatically alter the natural history of treated PD and in this sense, they could be seen to be disease modifying, as discussed by Kieburtz et al. (2021) [10].

THE CLINICAL HOPE AND CHALLENGES

If we start from this position of understanding, then we need to ask: “What is the clinician/investigator hoping to achieve (and not achieve) with such therapies?” This can be summarized as follows:

(i) better, more stable control of many of the core motor elements of PD for many years;
(ii) avoidance of off target effects as seen with current oral dopaminergic drugs used to treat PD, including their neuropsychiatric, cognitive, and autonomic side effects;
(iii) avoidance of long-term side effects seen with the pulsatile stimulation of the dopaminergic network using oral L-dopa preparations, especially the development L-dopa induced dyskinesias and the additional treatments that these necessitate when severe enough; and,
(iv) avoidance of indwelling cannulae or wires/batteries which characterize the currently used advanced therapies for PD and the risks these bring with them of infection and delivery failure.

In order for this to become a reality, several key questions need to be answered for these ATMPs which includes whether they can:

• work as well as those dopaminergic and related therapies that are currently available in the clinic now and do so over many years (see, e.g., [11]) and/or provide additional benefits not offered by conventional dopaminergic drug therapies;
• be manufactured consistently and in a way that makes them affordable to health care systems. This would seem to be possible in theory with dopamine cell therapies given that their manufacture only involves a relatively short and highly efficient 16-day differentiation protocol [12];
• help a significant proportion of PD patients;
• not produce their own significant side effects that require other invasive interventions, such as has been seen with the development of graft induced dyskinesias with fetal ventral mesencephalic allotransplants [13];
• be shown to not stop working soon after being implanted by succumbing to the pathogenic processes underlying PD. In this respect, it has been shown that fetal ventral mesencephalic grafts acquire Lewy body pathology over time post grafting- albeit at a rate that does not appear to adversely affect their function [14, 15];
• be derived from ethically acceptable and properly consented sources which is important especially for stem cell derived dopamine cell therapies;
• be delivered using devices that are CE approved and ideally do not require complex operational systems for them to used, such as intraoperative MRI.

If all this can be realized, then we will have useful new “dopaminergic” treatments for PD which ultimately could be combined with true disease modifying therapies targeting the underlying disease process and the non-dopaminergic aspects of this condition.

THE REALITY OF CLINICAL TRANSLATION AND ITS CHALLENGES

The regulatory landscape for ATMPs is continuously evolving and brings with it many complexities, which vary to some extent depending on which regulatory agency one is operating under, e.g., U.S. Food
and Drug Administration (FDA) versus European Medicines Agency (EMA) or Pharmaceuticals and Medical Devices Agency (PMDA). In this section, we aim to highlight some of the challenges faced when translating any ATMP to a first in human clinical trial for PD and which any investigator will have to engage with at an early stage of ATMP development and translation.

In order to set up and conduct a clinical trial of an ATMP, there are many processes which need to be followed, each dependent on the country-specific regulatory guidelines. There is not a ‘one fits all’ approach to the set-up, approval, and conduct of such trials. In a survey of European-based ATMP developers, it was found that challenges were faced in the following areas: regulatory, technical, scientific, financial, clinical, human resource management, and others (including intellectual property and public perception) [16].

In Table 1, we outline in further detail some of these key challenges.

Ownership and use of the ATMP

This can be one of the key challenges, especially around the intellectual property landscape with respect to the ATMP and the security of that position enabling long term investment for the trialing of it with a view to taking it to market. If the ATMP uses human-derived cells then the following key issues will need to be resolved:

- Adequate consent for use of the cell line obtained prior to collection of donation, including donor screening and testing;
- Whether the product can be used in different countries, e.g., there are some restrictions in the US with human embryonic stem cell products derived in countries known to have had cases of variant Creutzfeldt–Jakob disease;
- The ownership of the cell product and the licenses associated with its use in preclinical work and clinical trials. It is important to have in place correct licensing agreements so the cell line can be used in both preclinical work as well as clinical trial(s).

Device

In order to deliver the ATMP, a suitable device may be needed, and ideally it should be one that can be used at all trial centers rather than one that can only be used at one site (with that hospital taking the responsibility for the use of that device locally). If different devices are being used at different centers, this will cause issues with merging of trial data further down the line.

The device may be CE marked or be an investigational device. The latter poses further issues, as the trial itself will then become an ATMP and device trial.

If planning to use a CE marked device, then one needs to ensure it is being used within its intended use. In general, if the device is being used outside of its approved intended purpose there may be a requirement for the ATMP trial to also become a clinical investigation of a medical device. There are some exceptions to this—for example, in the event a healthcare institution is using a device outside of its intended purpose without the knowledge of the device manufacturer, a clinical investigation may not be required. However, even this could have some legal implications.

Trial design and approval

Many sites worldwide are yet to conduct any trials using ATMP products and therefore this is unknown territory. It is important to define from the outset, the sponsor of the clinical trial and the sites that will contribute to the trial. The approval process across the different regulatory authorities worldwide varies and therefore it may be necessary to bring in expertise from consultancy firms who have knowledge of relevant regulatory authorities. Some examples of regulatory differences between countries include: classification of device by a regulatory authority; or requirement for use of GMP facilities for processing of a cell product (if needed) prior to implantation. In addition, whether the trial should have an imitation surgery/sham early from the outset is another important issue that is often seen differently by the FDA compared to say the EMA or PDMA.

Getting a trial site started

The sites need to have adequate knowledge and experience in delivering similar therapies previously or willing to undergo training. It is important to check that they have access to the facilities required to conduct the clinical trial; this can include specialist surgical suites and/or specific scanners. In some parts of the world, this infrastructure is well developed, e.g., alpha stem cells clinics in the U.S. [17], but in most countries such networks do not exist.
| Area                  | Challenges                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ownership & use      | Product owner  
License to use the product in preclinical development and clinical trial  
If the product is human-derived, was the right consent obtained initially to allow the product to be used in the way planned?  
If the product is human-derived, are full traceability records available? |
| Preclinical testing  | Testing requirements (e.g., biocompatibility, toxicology, packaging sterilization, sterilization validation)  
Who will perform the testing? Are there specialists available in the type of testing required?  
Training requirements for the testing, particularly if outsourcing (e.g., to a contract research organization (CRO))  
Budget for testing (device alone and device in combination with the product)  
Completing write-up, particularly documentation required for regulatory submissions  
Publishing the preclinical studies prior to the trial starting so that the wider community can access the key data underpinning the trial, thus ensuring transparency of what is being done and why |
| Manufacturing        | Site of manufacturing  
Requirement and availability of GMP facilities, and is one required for the making up of the final product at trial site?  
Storage of product until use (e.g., at manufacturing or clinical trial site) |
| Regulatory           | Different regulations across countries - so is an international trial worth pursuing initially?  
Availability of approved devices that could be used to deliver the ATMP  
If there is a device available: is it CE marked (or equivalent) to be used in the way that is being proposing to use it?  
If the device is not CE marked for this use: who owns the device, and will they support the device being used in a new way? Alternatively, is it possible for you to take on the expansion of its use?  
Can the device be used under hospital exemption, or does the planned trial also include a clinical investigation of the device?  
Combination product vs. separate therapy and device. If separate, capacity to support regulatory applications  
Budget for regulatory application(s) |
| Sponsorship          | Sponsor organization for the trial (considerations need to be made for multi-site, different countries)  
Experience of the sponsoring organization in sponsoring trials using ATMPs and/or investigational medical devices, if applicable |
| Regulatory support   | Availability of a clinical trials unit and oversight of the trial  
Potential outsourcing to specialist regulatory consultants, and the budget to support this |
| Trial assessments     | Trial assessments to be performed  
Need for long-term follow up of patients in receipt of products that are given in an irreversible fashion (e.g., gene injections or cell implants to the brain) ideally with declaration of intent for brain donation and the establishment of some form of trial registry for storing such data |
| Site set-up          | Number and location of trial sites including whether all sites will undertake patient assessments and grafting or just a subset will perform the transplant surgery  
Use of participant identification centers (PICs) (particularly if necessary equipment/facilities are limited)  
Additional site-level reviews (e.g., ATMP committees)  
Availability of necessary resource/equipment (including imaging) |
| ATMP requirements     | Site capability to release an ATMP therapy  
Requirement for local GMP lab (e.g., for storage and/or handling of ATMP) and associated costs  
Experience of surgeon experience in performing surgeries with ATMP therapies, use of devices to be employed in the trial +/- training to do this |
| Experience           | Additional safety reporting requirements  
Data capture and monitoring | Data capture systems, particularly for international studies where sites may have different regulations  
Experience of monitoring for ATMPs/medical devices trials, and capacity to support these additional requirements |
| Archiving            | Need for longer-term archiving and associated costs |
| Budget               | Ensure adequate funding to cover all costs, for pre-clinical, clinical and long-term follow-up. |

Additionally, sites must be aware of additional resourcing, which is likely to be greater than that for conventional clinical trials of investigational medicinal products (CTIMPs). Trials of ATMPs are subject to additional safety reporting (as further outlined below), extended follow-up of participants, and longer-term archiving requirements—all of which has budgetary implications.
Monitoring and reporting of the trial

For ATMPs, there is an enhanced requirement for safety reporting to the regulatory authorities. It is imperative when conducting a trial across countries with different regulatory authorities that there is a central reporting process to capture the safety events from the trial. This must also include robust processes to inform all trial investigators, plus any trial committees (i.e., trial steering committee/data and safety monitoring board), sponsor, and funder representatives.

Budget

As with any trial, it is vital to get sufficient funding secured and in place, including adequate allowance for additional costs through the course of trial set-up and particularly through the preclinical development of the ATMP product and device if required. There are additional costs involved specifically for trials of ATMP products, such as use of GMP facilities, regulatory costs, and extended archiving.

CONCLUSION

The taking of an ATMP for patients with PD through to clinical trials is complex and from an investigator’s perspective there are two main questions: why are you doing it, and do you understand what is needed to conduct a clinical trial with that product? Thus, it is critical that the rationale for the therapy is clearly understood along with what competitive advantage it could ultimately bring to PD patients. There is no point pursuing such therapies if the improvement is not equivalent to or better than that which can already be achieved with existing therapies. At the present time, the therapies being considered in this space are ones looking to better deliver dopamine to the striatum and the reasons as to why this approach is of merit have been briefly laid out. However, as we have also summarized, the investigator in addition has the responsibility of deciding how they will move that therapy to a trial. This is not straightforward and requires considerable time and input from a large number of specialists as well as a significant budget. As such pursuing such ATMPs is a major undertaking and those investigators seeking to do this should understand the complexity and responsibilities that this brings with it not only for their own work but the field more generally.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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