Bringing Advanced Therapies for Parkinson’s Disease to the Clinic: The Patient’s Perspective

Soania Mathur a,∗ and Jon Stamford b

a UnshakeableMD, Oshawa, ON, Canada
b Gentleman Neuroscientist and Independent Parkinson’s Advocate

Accepted 5 April 2021
Pre-press 3 May 2021

Abstract. There is an urgent unmet need in the Parkinson’s disease community—advanced therapies to modify the inevitable decline that occurs in those affected by this progressive neurodegenerative disease for which there is no cure. This will require collaboration from all stakeholders and central to those partnerships are patients themselves. But participation in clinical trials and clinical use of advanced therapies have their own risk profile above and beyond standard therapeutics as evidenced by past invasive procedures. Therefore, it is of utmost importance that clear, evidence-based information about these potential treatments be clearly communicated by those exploring their use to ensure safe and informed participation from the patient community. Likewise, patients must weigh the benefits of these treatments their limitations and risks in order to truly give informed consent to participate in bringing these treatments to the clinic. Here we explore these issues from the patient perspective.

Keywords: Parkinson’s disease, advanced treatments, clinical research, recruitment, patient-centered, gene therapy, stem cell replacement, patient risk

INTRODUCTION

Parkinson’s disease (PD) has been known for over 200 years since its first description by the apothe- casy surgeon James Parkinson in 1817 [1] with the first medication to treat this disease, and still considered the gold standard treatment, levodopa, being developed 150 years later.

Since the pivotal findings that dopamine was the principal neurotransmitter in the basal ganglia and that elevation of its levels by the administration of levodopa could ameliorate symptoms of PD, dopamine has been central to drug development. Drugs that elevated dopamine function improved motor symp- toms while those that decreased function exacerbated or precipitated PD. With such a clear association, historically there had been little incentive to look further afield.

Although dopamine replacement continues to be life changing for many patients, allowing them a greater degree of functioning and symptomatic relief, at least in the earlier stages of disease, the historical focus on dopamine has been in some ways a barrier to progress. Not only has there been no drug better than levodopa developed in more than 50 years but it also diverted attention from the nonmotor symptoms of PD which we now know account for a significant component of the quality-of-life burden for patients and often involve other neurotransmitter systems. Recognition of the complex interplay between the
efficacy and unwanted side-effects of existing drugs, a greater understanding of the whole-body effects of the disease and the need for a therapy that can stem the progression of PD, are providing new therapeutic goals.

The last 20 years have seen huge strides in our fundamental understanding of the pathophysiology of PD. In particular, the diversity of neuropathological changes and advances in our genetic understanding of this disease have led to more research pursuits. Such an extensive diversification promises commensurate expansion of the number of targets available for the development of new therapeutics. Most laboratory bench scientists working in this area are understandably optimistic. Despite this, and acknowledging the length of the drug development process, it still remains the case that this evolving understanding of the basic neurochemistry has not been reflected in a similar expansion of the number of new drugs or treatments. There is a substantial dichotomy between bench and bedside.

WHAT ARE ADVANCED THERAPIES FROM A PATIENT PERSPECTIVE?

A quick dip into the literature shows that the term ‘advanced’ therapy is widely used but less clearly defined. As Humpty Dumpty said to Alice, “When I use a word it means just what I choose it to mean—neither more nor less.” What defines an ‘advanced therapy’? For patients and for the purpose of this paper, a reasonable definition of an ideal advanced therapy is one which addresses one or more unmet needs of patients not covered by existing therapies, treatments with a novel mechanism of action and most importantly an intervention that has the potential to be disease modifying.

But current best medical and surgical treatments for PD are all symptomatic in nature, not long-term solutions. Many of what we consider advanced therapies involve different routes of administration, and alteration in drug pharmacokinetics, or novel surgical techniques leading to reduced side effects and greater efficacy. Those already licensed include deep brain stimulation (DBS), levocarbodopa intestinal gel [2], focused ultrasound ablation [3], and subcutaneous apomorphine infusion [4].

Surgical techniques aside, the remaining advanced treatments are not novel from a disease target perspective. Firstly, apomorphine is not a new drug. It acts on the dopaminergic systems like every other dopamine agonist. Secondly, recognizing that it has a short half-life and therefore is suited to pump administration, although helpful, does not reflect a significant change in the way we approach this disease. The same applies to levocarbodopa intestinal gel. Although the novel delivery mechanism for these treatments has its advantages in managing the unreliable pharmacokinetics of oral medications, both apomorphine pumps and levodopa intestinal gels act on the dopamine systems and therefore are not novel in terms of targeting new pathophysiology or modifying the trajectory of this disease.

Slowing the rate of decline, stopping the progression of PD or, better still, reversing the symptoms are perhaps the principal aspirations of patients. In simple terms, patients want to be able to live better and longer. These are not necessarily the areas reflected in the research landscape. It is perhaps significant that of 28 phase 3 clinical trials in PD registered in January 2020, immediately prior to the coronavirus pandemic, 25 were solely addressing symptomatic relief [5]. But there are more advanced treatments coming down the pipeline including gene therapy [6] and certain types of cell transplantation such as stem cells [7]. These advanced treatments hope to benefit the patient community but first must survive the rigors of clinical trials.

As these trials continue to progress through the developmental pipeline, there will be greater need for patients to become involved. Despite even optimal efforts, the progressive neurodegeneration that is the basis for this disease, continues unabated and symptomatic management cannot mitigate the end stage of its progression. If we want to impact the inevitable course of PD, it is important for the patient community to support the development of therapeutics that can potentially modify or cure this disease. However, participating in this research, as vital as it may be, harbors many questions.

PATIENT CONCERNS REGARDING ADVANCED TREATMENTS

The need for advanced, particularly disease modifying treatments has been identified. For the purposes of this paper, we will focus on gene therapy and stem cell infusions, the two principal treatments that seem to qualify as advanced therapies by the criteria laid out above.

Gene therapy is directed towards replacing or modifying mutated genes responsible for neuronal loss and lack of dopamine production. They are
directed either towards dopamine restoration and symptomatic therapy or disease modifying, slowing the course of degeneration via neuroprotection (neurotrophic factors) [8].

Cell transplantation, which began with adrenal cells in the mid 1980s [9] addresses the main cause of motor symptoms—destruction of nigrostriatal dopamine neurons—by replacing cells lost with human embryonic stem cells, human induced pluripotent stem cells or human fetal mesencephalic tissue [10]. Each protocol has advantages and limitations, but all require invasive brain surgery for delivery to their site of action.

Although promising, there are concerns with these potential treatments. For example, advanced therapies face the challenge that PD is not homogenous but instead a multi-faceted neurodegenerative disease involving multiple neurotransmitters and systems. The advanced therapies currently being studied are directed mainly towards the brain’s dopaminergic function. While this may alleviate motor symptoms, it will likely not improve the non-motor symptoms which consistently compromise patients’ quality of life [11]. That is the ultimate challenge – to address the multiple motor and nonmotor disease pathways that result in PD [12].

In addition, neither therapy is obviously able to address the still unknown cause of PD. Therefore, the potential exists that the insult causing PD will continue to progress, the pathology will continue unabated rendering a treatment directed for example, at cell replacement, to eventually become ineffective, potentially requiring the procedure to be repeated [13]. Early work with cell replacement found better long-term outcomes and implant survival in MPTP-injured individuals than in PD patients.

Also, whatever pathology leads to neurodegeneration, significant damage precedes the onset of symptoms by several years. By the time a person begins to experience signs of PD, up to 80% of the nigrostriatal dopamine neurons have been destroyed [14]. For neuroprotective treatments such as gene therapy to be successful, efforts would have to be directed to those in the pre-motor or prodromal stage or as early as possible in the disease trajectory. In this case these therapies may not be an option for those later in their diagnosis [15] leaving those advanced treatment options out of reach for those in advanced stages of disease when the effectiveness of standard medications fails.

The other principal shortcoming of these therapies has already been mentioned—they are highly invasive, requiring complex stereotactic surgery, general anesthesia and extensive perioperative care. In the context of clinical trials, there is also the additional possibility that the patient may undergo all of the above yet still fall into the placebo-controlled group. This doesn’t always sit well with patients who question the extent to which the control group must go in pursuit of ultimate scientific validity [16]. What is ideal scientifically is ethically much less comfortable.

In addition to the invasive nature of the procedures themselves, there is also concern about reversibility of the procedures, or more accurately their irreversibility. With all other existing treatments, including DBS, the treatments can be reversed or at least stopped. If the medication causes a strong adverse reaction, cessation usually alleviates the problem. Even in DBS, the current can simply be switched off. However, stem cells implanted in the wrong region cannot be repositioned. And any factor which modifies genomic information always has the concern of possible carcinogenicity or teratogenicity.

Put together, the invasive nature of the procedures and the irreversibility of the outcome, these are significant factors influencing patient decision-making on whether to participate in such a clinical trial. But above all, whether correct or not, patients have a higher expectation of benefit from more complex advanced procedures [17]. This is a clear learning objective for the scientific/medical members of the PD community. Patients are disinclined to submit to invasive procedures without clear reassurances of commensurate benefit. These reassurances need to be based on accurate information, hard facts and not expectation management.

**MAKING THE DECISION**

Yet despite the concerns, advancing the treatment of PD is urgently needed by the PD community. It is important to learn from past experience with invasive therapeutics in order to determine the safest and most ethical way of pushing the research forward.

Take DBS for example, an accepted advanced therapy for PD that involves invasive surgery and is targeted mainly toward motor symptoms that become unresponsive to best medical treatment. Over the course of 20 years, the technique has evolved from experimental investigation to accepted treatment [18]. Despite the limitations and risks, long-term follow up has yielded high patient satisfaction. Most DBS patients would repeat the procedure or
recommend it to others despite the general worsening of axial and mobility symptoms as well as continued nonmotor issues [19, 20]. In order to undergo this advanced treatment, there is a strict protocol for selecting appropriate subjects to minimize potential poor outcomes and an extensive educational component to the process. This type of due diligence serves as an example of how to manage patient expectations and leads to a clearer understanding of the advantages as well as potential limitations of this procedure. A similar type of detailed and thorough education of the patient of all possible benefits, risks and limitations must take place when recruiting for clinical trials as well. Patient oversight in participation in clinical trial development and recruitment can help develop decision aids or tools that impart the information needed.

So, what is the solution? How can the patient community be engaged in bringing advanced therapies to the clinic? One would like to believe that the acceptability of advanced therapies will lie with the principal and most invested stakeholders—patients themselves. The same goes for clinical trials. Given the complicated nature of advanced therapies compared to standard medical treatment, careful and comprehensive information, easily understood and explained, must be shared with patients so that consent is truly informed. Although this sounds simple it is in fact fraught with pitfalls.

Informed consent is the bedrock of all medicine whether trial or practice. Yet informed consent is influenced by many considerations, including age, responsibilities, family support, cultural influences, severity of illness, comorbidities and personality. Patients must ask themselves, is there a role for these advanced therapeutics given their potential benefits weighed against their limitations and risks? Can the cost and risk be justified compared to advancing standard therapeutics? Each patient must make a personalized choice that is tailored to their own disease, their stage of disability and quality of life. Where the patient is in their disease trajectory also influences the consent process. The kind of procedures to which a newly diagnosed patient might submit are probably very different from those acceptable to a patient with say 20 years of experience with PD, consent being guided by past disease experience and current clinical status.

Decision-making in general, is a matter influenced by many interacting phenomena. Some people are risktakers others are risk averse. Much has been written about the supposed “PD personality”, characterized by high levels of neuroticism, highly risk averse, avoiding situations of novelty and danger [21]. One might anticipate that such a cohort would be disinclined to participate in comparatively risky trials or to readily accept advanced but invasive technologies, but desperation is always a powerful incentive as evidenced by the Nilotinib example. Here misinformation resulted in a significant increase in off-label prescribing, a concerning trend given the toxicity and danger of this black-labeled medication [22]. When much needed safeguards are not in place, when the information needed for patients to make rational and appropriate decisions regarding their care, is not communicated, the results can be dire. Decisions are made not based on factual data but predicated on an intense desire to halt the inevitable decline into disability.

It is worth also acknowledging the role of medication as a factor in determining the validity of “informed consent”. Any potential recruits to a trial of an advanced therapy will not be drug naive or on minimal intervention. Far more likely the patient will be on many drugs, the majority of which will act on dopamine systems beyond the nigrostriatal pathway to the basal ganglia. Many PD patients take dopamine agonists as part of their therapy. These are well-known because of impulsivity and high-risk behaviors [23]. Posing such patients with the opportunity to participate in a high-risk study for instance, presents problems. Leaving aside the obvious consideration that the data will be biased towards a high-risk cohort, there is the additional question of whether consent to participate in the trial is genuinely informed and therefore valid or compromised by judgement impairment [24]. This is an ethical issue, probably outside the scope of this review.

**CONCLUSION**

The ultimate unmet need for those living with PD is a cure. Although it may be difficult to assert that any of the current advanced therapies being proposed are curative, changing or reversing the trajectory of this disease must remain a priority. But as important as it is for the research community to continue the search for disease-modifying treatments and ultimately a cure, this important work cannot proceed without the support and involvement of an informed and empowered patient community.

Both authors of this paper are scientists as well as patients. Patient acceptance of new advanced therapies cannot be taken for granted either at an individual
or collective level. Patients may make decisions that, viewed in isolation, seem capricious, falling outside the envelopes of expectation. In this context it is perhaps worth reflecting on the greater degree of investment by patients in therapy both existing and advanced. An unexpected negative outcome from a trial will always generate publishable data. For the patient such an outcome may be crippling or worse. As scientists, we can readily recognize value in some advanced therapies. Speaking however as patients, the arguments may seem much less persuasive when one gambles with one’s own health. And this decision must lie with patients.

Too often patient involvement is considered as an addendum to a project or clinical trial. Patients feel disempowered by what smacks of tokenism. Projects should involve patients from the very beginning. Ideally the initiatives for instigation of the project should come from the patients. Recognizing and endorsing patient centrality will go a long way towards ensuring uptake of advanced therapies. Good information flow in both directions and consequently understanding and empathy are essential. That involves both patient and scientific education to prevent waste of research investment. As once said in the context of education but equally applicable here, “if you think education is expensive, try ignorance.”

**CONFLICT OF INTEREST**

The authors have no conflict of interest to report.

**REFERENCES**


