Disease modifying treatments for Parkinson's disease – an update

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Abstract
An improved understanding of the pathological processes leading to neurodegeneration in Parkinson's disease (PD) is leading to the development of a number of disease modifying agents. These include both novel and repurposed drugs. Some of these disease modifying therapies act on cellular targets that have been identified by genetic mutations, while others act on other cellular process which we know are affected in PD. This review provides an update on the progress in the field, and highlights some areas of special interest.

Introduction

Current treatments for Parkinson's disease (PD) are primarily symptomatic and consist mainly of dopamine replacement therapy, and deep brain stimulation. These treatment strategies have gradually improved over the last few decades, and further advances are underway [1], but they do not address the fundamental problem of progressive neuronal loss in the nigro-striatal pathway and other brain regions. New disease modifying treatment approaches are in development that target the cellular events leading to neuronal loss, in order to slow or reverse this process. While this would be transformative, the optimal approach to achieve this is clouded by several unanswered questions. We do not fully understand the function of normal, soluble alpha-synuclein. Furthermore, the exact role played by pathological aggregates of alpha synuclein in pathogenesis is debatable. We do not know whether treatments targeted against genetic subtypes of PD will be effective in sporadic PD [2]. Overall, the research field is very active, studying targeted therapies related to genes, and treatments related to metabolism/mitochondrial function, inflammation, oxidative damage, and neurotrophins [3]. In this review, we summarise the current developments in this field, with a focus on treatments that are in clinical trials. We have selected highlights from a comprehensive list of ongoing studies [3].

Alpha Synuclein

Treatments designed to modulate the aggregation and deposition of alpha synuclein are clearly promising, given the almost universal detection of this pathological process in PD. This approach builds on extensive knowledge obtained since the identification of alpha synuclein gene mutations as the first genetic form of PD, and the detection of dense alpha synuclein deposits within Lewy bodies. Treatments in development aim to prevent or remove excessive alpha synuclein that exists in pathological 'clumped' form of oligomers and fibrils, in distinction from the normal unfolded form of monomers and tetramers. These toxic forms of alpha synuclein impair degradation pathways and cause dysfunction of mitochondria and endoplasmic reticulum [1]. Clinical trials involving antibodies against pathological alpha synuclein are currently in Phase 2. This involves either passive immunisation e.g. infusion of a monoclonal antibody (mAb), or active immunisation such as with PD01A, where the patient's immune system generates antibodies against abnormal alpha synuclein. Prasinezumab (PRX002) is still in development, despite a negative primary outcome in a phase 2a study, on account of a positive secondary outcome of reduction in motor function decline. Cinpanemab (BIIB054) failed to meet its primary and secondary outcomes and has been discontinued at present. Another approach is the reduction of alpha synuclein synthesis using anti-sense oligonucleotides, but this may disrupt its normal physiological role in synaptic transmission and intracellular trafficking [1]. Enhancing the clearance of alpha synuclein, which occurs via the ubiquitin proteasome and autophagy-lysosomal pathways, is also a potential treatment approach, with an aim to restore the balance between benign and toxic forms of alpha synuclein [1]. One strategy is the therapeutic inhibition of the tyrosine kinase ABL, an enzyme that is pathologically activated in patients with PD. Such inhibition would prevent the phosphorylation (and thereby inactivation) of parkin, which normally contributes to cell clearance processes. Nilotinib – an ABL inhibitor used in haematological cancer – has shown some promise in animal models and a pilot study of PD. However, it was ineffective in later stages of PD in one recent study [4]. Radotinib, a molecule from the same class and with higher brain penetration, is also under study [3]. Small molecule inhibitors of alpha synuclein aggregation have the advantage of good brain penetration, and include UCB0599 and anle138b [3,5]. Memantine, a

Table 1. Drugs in advanced stages of development that target molecular pathways not identified through genetic mutation

Drug name/class	Postulated mechanism of action	Stage of development
Glucagon like peptide 1 receptor agonist, eg. exenatide [17,18]	Neurotrophic	Phase 3
Urso-deoxycholic acid [19]	Increased signalling in the Akt pathway	Phase 2
Deferiprone [20,21]	Iron chelation to reduce iron deposition in substantia nigra	Phase 2

NMDA receptor antagonist, reduces intercellular propagation of alpha synuclein [6], and is in a phase 3 study as a potential disease modifying agent using advanced imaging [3].

Glucocerebrosidase

Several new treatments are in clinical development that target mechanisms related to lysosome function, including the enzyme glucocerebrosidase (GCase) that resides largely within the lysosome. Pathological variants in the GBA gene which encode this enzyme are the most common genetic risk factor for PD, being present in around 10% of cases [7]. GCase deficiency has also been observed in patients with sporadic PD [8], so such treatments may be effective regardless of genetic status. The aim is to restore normal lysosome function which is expected to have positive impact on cellular processes, including pathways that assist the recycling or safe disposal of alpha-synuclein [7].

Imiglucerase, a recombinant DNA enzyme used successfully in Gaucher's disease (resulting from different forms of GBA gene mutation) reverses the abnormality in lysosomes in a genetic model of PD [9]. However, treatments for Gaucher's do not cross the blood brain barrier (BBB) and therefore alternative approaches are being developed for PD [10,11]. These include enzyme replacement therapy, enhancement of the activity of available enzyme, and substrate reduction therapy. Gene replacement therapy using vectors such as adeno-associated virus (AAV) has shown success in reducing alpha-synuclein accumulation and neurodegeneration in animal models [11]. The PROPEL trial is a phase 1/2 study exploring AAV treatment using imiglucerase in GBA-positive PD. This viral vector is delivered to the brain using magnetic resonance guided focused ultrasound to open the BBB and permit CNS penetration. Another approach is the use of pharmacological chaperones, whose molecular size is small enough to cross the BBB [11]. These improve cell function by assisting substrate proteins to fold correctly, aiding in intra-cellular transport and improving protein degradation. Chaperones can be administered orally, and are generally not expensive [11]. Ambroxol is an expectorant with promising initial results as a PD therapy, and among the pharmacological chaperones is the farthest down the drug development pipeline. In phase 2 clinical studies Ambroxol had a good safety and tolerability profile, and also had good CSF penetration and target engagement [12]. Substrate reduction therapy is another potential approach, wherein reduced glycolipid production results in a rebalancing of the ratio between enzyme activity and substrate. Glucosylceramide synthase inhibitors with good brain penetration are under investigation, following encouraging results in animal models. Venglustat is one such inhibitor that unfortunately failed to show efficacy in a recent trial in GBA-positive PD cases [13].

Leucine Rich Repeat Kinase (LRRK)

Kinase inhibitors which act on LRRK are in development as potential disease modifiers in PD. Mutations in the LRRK2 gene are the most common cause of dominantly inherited PD (10-15%), and are present in some patients with sporadic PD (1-3%, though higher in some populations). LRRK2 mutations in contrast to GBA mutations can be both causative i.e. a single mutation with a large effect, and a risk factor i.e. a single mutation with small effect size and therefore by itself not sufficient to cause disease. Kinase inhibitors are designed to block abnormally increased LRRK2 activity, due to toxic gain of function mutations, rather than loss of gene product [14]. Increased LRRK2 activity is seen, both in cases with LRRK2 mutations, and cases with sporadic PD [15], so treatments could have widespread benefit. LRRK2 plays a role in striatal synaptic transmission, mitochondrial function, microtubule dynamics and ubiquitin proteasome function [14]. Therefore treatments targeting LRRK2 could have an impact on multiple cellular processes; one proposed mechanism is to prevent the LRRK2-mediated phosphorylation of alpha synuclein, which increases its aggregation, and contributes to its propagation along neurons [14]. However, the LRRK2 gene is also expressed in immune cells, kidney, and lung, so monitoring of the effects of kinase inhibition is required to check for adverse effects on other organ systems [15]. Results from a phase 1 study in healthy controls and patients with PD have found no safety concerns with DNL151, a LRRK2 inhibitor, when administered for a 28 day period [16]. Phase 2 and 3 studies are in the pipeline.

Additional treatments

In addition to the treatments outlined above, there are other promising drugs which are in advanced stages of development, and summarised in Table 1.

Conclusion

Current approaches for disease modification are multi-faceted and include both novel and repurposed drugs. While it is impossible to predict which of these approaches will be the most successful, we can surely be optimistic, based on the scale of work that is underway.

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