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CURRENT STATUS OF NON-DISEASE MODIFYING GENE THERAPY IN PARKINSON'S DISEASE

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ABSTRACT:

Parkinson's disease (PD) is a chronic progressive neurological disorder characterized by bradykinesia, tremor, muscular rigidity, and postural instability. The world-wide prevalence is expected to rise further with increasing mean age. Theoretically, if all desired elements required for dopamine synthesis are functionally available, need for exogenous L-DOPA administration can be eliminated or markedly reduced. However, lack of effective long-term treatment has led to extensive gene therapy research focusing both on disease modifying as well as non-disease modifying aspects. Since genetic lesions are found in both familial as well as sporadic PD cases, the principle of introducing a normal gene to cure a disease can also be applied in PD. Success in effective gene delivery to the target brain regions and its tolerability owing to negligible immune response against the vector has further encouraged the work. The likelihood of gene therapy becoming future and true cure for PD is very high. This commentary describes status of non-disease modifying gene therapy in PD.

KEY WORDS: Parkinson's Disease, gene therapy, non-disease modifying, dopamine

Parkinson's disease (PD) is a chronic progressive neurological disorder of old age. It is characterized mainly by bradykinesia; other features are tremor, muscular rigidity, and postural instability. The world-wide prevalence of 200 cases per 100,000 populations is expected to rise further with increasing mean age in the western world. The basic pathology is loss of dopaminergic neurons that starts in medulla oblongata, olfactory structures, and pons (Braak stages 1 & 2). Symptoms appear when it spreads to the substantia nigra, other midbrain nuclei and limbic areas (Braak stages 3 & 4). In Braak stages 5 and 6, primary cortex is also involved. L-tyrosine is an amino acid which is converted by tyrosine hydroxylase (TH) to L-DOPA which subsequently is converted to dopamine by aromatic acid decarboxylase (AADC).[1] Theoretically, if all desired elements required for dopamine synthesis are functionally available, need for exogenous L-DOPA administration can be eliminated or markedly reduced. Currently available agents for symptomatic treatment include: levodopa/carbidopa, monoamine oxidase (MAO) – B inhibitors, ergot and non-ergot derived dopamine agonists, Catechol-O-methyltransferase (COMT) inhibitors and amantadine.[2]

Gene therapy aims towards modifying or manipulating the expression of a gene or to alter the biological properties of living cells for therapeutic use. It can be achieved by designing DNA or RNA constructs, gene transfer vectors, delivery of genes into the target cells, and regulation of transgene expression. Success in rodent studies indicates that gene therapy may be relevant in PD as well. Amongst several gene delivery methods, serotypes of adeno-associated virus (AAV) and lentivirus (LV) are considered primary vectors for gene introduction.[3] Since, genetic lesions are found in both familial as well as sporadic PD cases, this principle of introducing a normal gene to cure a disease can also be applied in PD. So far, 18 different chromosomal aberrations termed as PARK loci have been identified.

Both non-disease modifying and disease modifying targets have been explored for possible gene therapy.

Non-disease modifying options aim at improving PD symptoms by normalizing abnormal firing of neurons in basal ganglia; this can be achieved by enhancing dopaminergic or GABAgenic enzyme apparatus. Current state of non-disease modifying gene therapy in PD is discussed below:

A decade earlier, following successful demonstration of vector-mediated AADC overexpression in animal studies, phase 1 clinical trials also reported improvement in symptoms measured by unified Parkinson's disease rating scale (UPDRS).[4] Currently, studies focusing on optimum dose and delivery are underway. The results of these studies will be helpful in initiating randomized placebo-controlled trials. Although results appear promising, AADC gene-therapy cannot be used as a sole treatment because it requires continuous L-DOPA administration.

Tyrosine hydroxylase converts L-tyrosine to L-DOPA and subsequently to dopamine by aromatic acid decarboxylase (AADC). Another enzyme GTP cyclohydroxylase 1 (GCH) catalyses the rate limiting step in tetrahydrobiopterin (BH4) synthesis; a cofactor for TH. Efforts have also been made towards enhancing all three TH, AADC and GCH enzymes. Animal studies in late 90s demonstrated increase dopamine production in striatum by using a mix of AAV-AADC and AAV-TH.[5] However, incorporating three different genes in a single vector is difficult. Therefore, either three AAV-vectors or lentivirus can be used to accomplish this goal. Using one or more modifications, improvement in dopamine levels and hence PD symptoms have been reported. Based on improvement in both dopamine production and improvement in PD symptoms, phase 1 trial focusing on LV-TH-AADC-GCH named as ProSavin was conducted. The authors have reported significant reduction in UPDRS scores along with acceptable safety profile. The baseline UPDRS score of 38 improved to 26 and 27 at 6 and 12 months respectively ($p=0.0001$).[6]

Decreased dopamine output in PD is also associated with increased glutamatergic activity from other brainstem loci.[7] The resulting motor symptoms can be ameliorated by conversion of glutamate to γ-amino butyric acid (GABA) by glutamic acid decarboxylase (GAD). After promising results in animal studies and phase 1 trials, a double-blind sham-surgery controlled randomized trial showed decrease in UPDRS scores by 8.1 and 4.7 in AAV2-GAD infusion and sham surgery groups respectively.[8] The follow-up study also showed persistent effect at 12 months[9] however, no new trials are underway to further explore AAV2-GAD therapy.

The knowledge of recurrent genetic abnormalities in familial form of PD provides opportunity to target these lesions with curative intent. Autosomal dominant form of PD requires inhibition of abnormal proteins. Two such targets α-synuclein and LRRK2 have been studied. In animal studies, up to 50% reduction in α-synuclein has been reported.[10] LRRK2 inhibition using RNA interference has also been successfully demonstrated in in-vitro studies. In an autosomal recessive form of PD, loss of function mutations in Parkin gene are associated with PD symptoms. Parkin coding AAV and lentivirus vectors have demonstrated improved neuroprotective effects in animal studies.[11]

Owing to extensive biochemical, biological, and genetic information about PD and lack of effective long-term therapy, gene therapy for PD has become an extremely important field of research. Success in effective gene delivery to the target brain regions and its tolerability owing to negligible immune response against the vector has further encouraged the work. Extended validation of effective therapies along with comparisons with well-known treatment modalities is required in Phase 3 trials. The likelihood of gene therapy becoming future and true cure for PD is very high. In upcoming years, based on efficacy and safety profile, AAV-GAD[8,9] and ProSavin[6] are likely candidates for inclusion in larger Phase III trials.

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