The Prospect and Challenges of Therapeutic Vaccines for Parkinson's Disease

Mufei Jiang[1, *]

[1]Wake Forest University, Winston-Salem, USA

* Corresponding Author Email: jianm22@wfu.edu

Abstract. Parkinson's Disease, the second most common neurodegenerative disease worldwide, still poses many problems in treatment, such as the side effects of medications and the lack of therapies for Parkinson's Disease's non-motor symptoms. This review discusses a novel measure of coping with the disease—the use of therapeutic vaccines to direct toward alpha-synuclein, a pathological hallmark of Parkinson's Disease. This review will primarily discuss UB-312, which had undergone a carefully conducted clinical trial, as an example of the therapeutic vaccines. The clinical trial demonstrated that UB-312 could elicit robust immune responses while being safe and well tolerated, suggesting a great potential for therapeutic vaccines in Parkinson's Disease treatment.

Keywords: Parkinson's disease; alpha-synuclein; UB-312.

1. Introduction

Parkinson's Disease, the second most common neurodegenerative disease after Alzheimer's disease, is a chronic, idiopathic disease with symptoms in both the motor and non-motor systems [1]. Symptoms in motor systems include tremor, slowness of movement, and rigidity, while symptoms in the non-motor system include breathing and respiratory problems, fatigue, and pain [2]. The symptoms worsen as the disease progresses over time. In pathology, PD is characterized by the loss or degeneration of dopaminergic neurons within the substantia nigra, accompanied by the formation of Lewy Bodies within these dopaminergic neurons. This neuronal loss leads to motor control impairment. Lewy Bodies, which are abnormal intracellular aggregates, contain a variety of proteins such as alpha-synuclein and ubiquitin, contributing to the dysfunction of neurons [1]. Every year, close to 90,000 individuals receive a diagnosis of PD in the United States alone, while globally, over ten million people are currently living with the condition [2].

Current treatments for PD include medications aimed at either depleting dopamine or mimicking its effects on dopamine receptors, surgical treatment, and exercise. Medications include levodopa, dopamine agonists, monoamine oxidase B inhibitors, and sometimes anticholinergics. The combination of levodopa with a DOPA decarboxylase inhibitor stands out as the most efficacious therapy for Parkinson's disease. The combination of levodopa with a DOPA decarboxylase inhibitor stands out as the most efficacious therapy for Parkinson's disease (in the US, carbidopa is used as the DOPA decarboxylase inhibitor). Carbidopa's slow blood-brain barrier passing rate enables levodopa to undergo conversion into active dopamine within the central nervous system [3]. The current argument for starting levodopa treatment early is that levodopa is more effective than other treatments and has fewer side effects in the beginning and that the duration of the disease and the amount of levodopa taken are more important factors in the onset of motor complications than the duration of levodopa exposure [4]. While there isn't a universal consensus, commencing levodopa therapy early in the disease progression is deemed appropriate. Nonetheless, for early Parkinson's disease, levodopa treatment should be limited to the minimum effective dosage. If there is an escalation in levodopa dose requirements, it's advisable to explore alternative therapies such as dopamine agonists [3].

Patients whose symptoms cannot be effectively dealt with oral medications alone may consider surgical and other advanced treatment options. Early in the course of PD, most patients' living condition is improved, and their motor symptoms are effectively controlled by medication. However, continued administration of dopaminergic therapies can lead to the development of dyskinesia and motor fluctuations in patients. Even in the early stages of the disease, medication side effects can

reduce the therapeutic efficacy for some patients. Ablative techniques, deep brain stimulation, and dopaminergic medication infusion devices are the current advanced treatment options. The effects of these therapies typically involve either continuous delivery of dopaminergic medication or the improvement of motor symptoms through specific stimulation or ablation of the motor circuit. Unsatisfactory control of motor symptoms usually drives patients to choose advanced therapies, though it is also common to observe positive as well as negative impacts on non-motor symptoms [5].

Exercise and physical activity may offer widely accessible, low-cost aids to the current PD treatments. Exercise has been shown to help delay the onset of PD and slow the disease's progression in earlier research exploring the connection between exercise and PD [6]. Exercise can also improve motor impairment, slow down cognitive decline, and improve quality of life. Treadmill training, dancing, tai chi, and other physical activities at different intensities have all been shown in randomized trials to alleviate the motor symptoms of PD [6, 7]. Several large controlled clinical studies have demonstrated that consistent exercise can enhance daily function in the early stages of PD, including bradykinesia, balance, and turning [6].

However, despite the current endeavors, therapies are still lacking for non-motor symptoms like cognitive impairment and sleep disorders, and motor symptoms such as freezing of gait, as well as autonomic nervous system symptoms [8]. In recent years, researchers have found a new path for treating Parkinson's Disease, which is the use of therapeutic vaccines. This treatment offers a great potential to effectively treat PD. This paper discussed the use of therapeutic vaccines in PD.

2. Mechanism of Therapeutic Vaccines for PD

Many investigations in the past 20 years have demonstrated that α-synuclein plays a crucial pathological function in both sporadic and hereditary variants of PD: The misfolding and aggregation of α-Synuclein are linked to the pathology of PD [9]. Besides the loss of dopaminergic neurons, another notable pathological feature of PD is the occurrence of Lewy bodies (LB), which are proteinaceous cytoplasmic inclusions found within neurons, along with dystrophic Lewy neurites (LN) that also harbor deposits of α-syn. In 1997, scientists established the initial connection between α-syn and PD when they identified point mutations in the SNCA gene in familial types of PD [10]. The identification of families harboring duplicate or triple copies of the SNCA gene further solidified the association between α-syn and PD, illustrating that elevated levels of the normal protein alone can lead to the disease [9]. Individuals with SNCA triplication demonstrate a heightened clinical phenotype (early-onset parkinsonism with dementia) compared to those with SNCA duplication (resembling idiopathic PD), highlighting a dosage-dependent correlation between the severity of the disease and SNCA gene amount. The genetic variability commonly observed at the SNCA locus represents a substantial risk factor for PD.

Research indicates that α-syn adopts diverse conformational shapes within a dynamic equilibrium in its native state, modulated by factors that accelerate or inhibit fibrillation. Mutations associated with the disease impact its folding and the dynamics of its aggregation and result in the abnormally extensive aggregation of α-syn. Laboratory studies have demonstrated that α-syn exhibits a dynamic equilibrium in vitro, wherein monomers initially aggregate into various small oligomeric species, which are stabilized by β-sheet interactions. Subsequently, these species further assemble into insoluble protofibrils of higher molecular weight and may transform into amyloidogenic fibrils similar to those present in Lewy Bodies (LB) [9]. Although the mechanism driving α-syn's shift from a normal form to a pathogenic form (i.e., the initiation of α-syn misfolding and aggregation) remains elusive, available evidence strongly indicates that therapeutic interventions targeting pathological forms of α-Syn hold promise. The presence of α-Syn aggregates in the form of LBs and Lewy neurites serves as prevalent neuropathological indicators in both familial and sporadic PD cases, underscoring the central role of α-Syn in the neuropathogenesis of PD [11].

3. UB-312: a Vaccine in Clinical Trial

As next-generation technologies advance, immunotherapy—a rapidly emerging field of medicine—can now create highly targeted vaccines against proteins associated with neurodegenerative diseases. For synucleinopathies, which include PD, very few immunotherapies have been developed, and only two of them are in clinical trials. One of the two immunotherapies is UB-312, a product using UBITh technology and designed to target α-syn. It can trigger an enhanced B-cell response and, in the meantime, evade detrimental pro-inflammatory T-cell responses [11].

3.1. The Design and Preliminary Success of UB-312

The UB-312 peptide was chosen after studying more than sixty α-Syn B-cell epitopes using guinea pigs [12]. UB-312 consists of a completely synthetic peptide derived from the C-terminal domain of α-Syn encompassing 10 residues. It is combined with an adjuvant comprising polyanionic Adju-Phos and phosphoguanine oligodeoxynucleotide (ODN). Researchers substituted the wild-type T cell epitopes with foreign, non-selective T-helper peptides using UBITh technology, and the peptides are covalently linked to the antigenic α-Syn peptides. The modification enhances UB-312's immunogenicity, ensuring a strong immune response targeting α-Syn rather than the carrier protein. The antibodies produced from guinea pigs immunized with UB-312 demonstrated high specificity for not only α-Syn oligomers but also α-Syn fibrils. Additionally, the antibodies exhibited precise recognition of abnormal α-Syn aggregate formations in postmortem brains affected by various synucleinopathies, including Parkinson's disease [12]. Moreover, immunotherapy strategies directed towards α-Syn have demonstrated efficacy in alleviating α-Syn pathology and functional impairments in mouse models of Parkinson's disease, leading to their progression into clinical trials [11].

3.2. The Clinical Trial of UB-312

3.2.1. Methods and Design

The results of the first clinical trial with UB-312 were published in 2022. This single-center trial evaluated the immunogenicity and safety of seven UB-312 treatment regimens using randomized, double-blind, placebo-controlled methodology. Seven treatment cohorts were randomly assigned to fifty eligible, healthy participants. Eight participants made up the lowest dose cohort, and seven participants made up each of the remaining cohorts. The dose of UB-312, which is the UB-312 dose level at week 1, week 5, and week 13, increases from cohort 1 to cohort 7 from 40, 40, 40 μg to 2000, 2000, 2000 μg. The study period for all eligible participants consisted of twelve weeks of medication and up to thirty-two weeks of follow-up, totaling a duration of 44 weeks. The study included both male and female participants who were between the ages of 40 and 85 and were generally in good health with no clinical conditions. From 30 days before screening until 8 weeks after the last administration of investigational product (IP), all medications that were not allowed—such as heparin or thrombolytic therapy, systemic corticosteroids, and any vaccination—was prohibited from use. Individuals with an allergy history were not allowed to participate. Laboratory testing, ECGs, neurological and physical examinations, vital signs, and adverse events were used to evaluate safety and tolerability. All participants had their brain magnetic resonance imaging (MRI) obtained during the screening process, and if the investigator considered it necessary for a safety assessment, the participants could request an unscheduled MRI. For seven days following each vaccination, all participants were instructed to record any systemic reactions or vaccination-site reactions.

Reactogenicity was evaluated by the adverse events reported by the participants. The results were recorded for potential use in additional assays in the event that the clinical study produced unexpected results. At week 1 (which serves as the baseline before vaccination) and at every visit after vaccination from week 2 to week 45, blood samples were taken. At week 1 and week 21, CSF samples were obtained.

The degree of immunogenicity was evaluated by measuring the concentrations of anti-α-Syn97−135 antibodies in blood serum and cerebrospinal fluid through ELISA-based techniques. As

an exploratory outcome, antibodies against the vaccine's constituents (CpG1 and UBITh1) were also evaluated. Further exploratory assessments comprised the evaluation of cytokine release from peripheral blood mononuclear cells, the concentrations of total and free α-Syn in these fluids, the levels of inflammatory cytokines in blood plasma and cerebrospinal fluid, and the antibodies binding to both monomeric α-Syn and oligomeric α-Syn [11].

3.2.2. Clinical effect of UB-312

Fifty healthy individuals were randomly allocated to be administered either UB-312 or a placebo for each treatment group. Except for one subject in cohort 2, who exhibited abnormal laboratory data at the beginning of the trial and was withdrawn from the trial after one dose of UB-312, all participants in cohorts 1 through 4 received three vaccinations as per the protocol. Cohorts 5 through 7 were stopped from receiving medication after a participant in cohort 6 experienced flu-like symptoms ranking grade 3. Vaccination with UB-312 up to a dose of 300,300,300 μg was proved be safe in general and well tolerated. No serious adverse events or deaths were reported. The clinical laboratory data and examination results did not show any trends that were clinically significant or treatment-emergent. There were no noteworthy patterns or alterations in the participants' inflammatory responses mediated by T-cells. The amounts of several biochemical indicators in the cerebrospinal fluid stayed within the normal range following UB-312 immunization, confirming the lack of CNS inflammation. Additionally, leukocytes and cytokines did not alter from baseline following immunization. 96% of the 193 treatment-emergent adverse events had mild severity. The investigator identified 96 adverse events that were possibly related to the treatment; 32 of these were reactions at the vaccinated site with 31 being headaches. The most common local reactions noted by the participants in the seven days following each vaccination were pain and tenderness at the vaccination site. 2 subjects experienced flu-like symptoms temporally associated with dosing. Following the administration of the second dose, one participant in cohort 6 whose dosage was 1000,1000 μg experienced fever and vomiting. The incident received a severe (grade 3) rating. Prior to the second administration of UB-312, the participant had already exhibited slightly higher amounts of C-reactive protein and erythrocyte sedimentation rate. Twenty-four hours following the second dosage, proinflammatory cytokines were measured and found to be within baseline ranges. This subject had high and rapidly developing antibodies targeting α-Syn, but not disproportionately higher than the rest of the cohort.

Before receiving the UB-312 vaccination, not a single person receiving UB-312 exhibited any noticeable antibodies directed against the target epitope, which is the synthetic α-Syn97−135 peptide. On the other hand, one individual in the placebo group had naturally occurring anti-α-Syn97−135 antibodies, which were detectable but low and stayed that way over the course of the investigation. Overall, UB-312 immunization elicited robust serum antibodies targeting the designated epitope, with antibody levels dependent on both time and dosage. Notably, all cohorts exhibited antibody increases by week 9, which occurred four weeks after the second vaccination. The concentration of anti-α-Syn97−135 antibodies reached its peak at week 17 before gradually decreasing. Even at week 45, mean serum anti-α-Syn97−135 antibody concentrations remained higher than baseline levels in three cohorts. For cohort 4 (300/300/300 μg), the biggest increase was observed at week 17, when the mean concentration of antibody in blood serum increased to 65.44 μg/mL. For the twenty-three individuals in cohort 1 to cohort 4 who received all three vaccinations, the overall seroconversion rate was 91.3%. Anti-α-Syn antibodies specific to target epitopes were found in CSF samples taken at week 21, but no antibodies were found in cerebrospinal fluid samples taken prior to vaccination. The average ratio of the cerebrospinal fluid antibody concentration to the blood serum antibody concentration at week 21 for participants with discernible cerebrospinal fluid antibodies was 0.2%. The immune response is highly targeted to the desired B-cell epitope, and when PBMCs were obtained before and after vaccination and stimulated with the antigen (the α-Syn peptide epitope), their ability to secrete cytokines revealed little to no T cell activation. As anticipated in healthy individuals, the amounts of α-Synuclein in blood plasma and cerebrospinal fluid remained constant following vaccination throughout the investigation. Dot blot studies of antibodies generated in healthy individuals who

received UB-312 vaccination revealed that the post-immunization serum IgG fraction recognized all variations of α-Syn. Notably, there was a higher signal intensity for α-Syn oligomers compared to its monomers for all examined concentrations.

In summary, in this inaugural human trial, UB-312 generated potent anti-α-Syn97−135 antibodies in a time- and dose-dependent manner, discernible both in blood serum and cerebrospinal fluid, while demonstrating a favorable safety profile and tolerability. The majority of TEAEs were mild and self-resolving, and there was no discernible difference in the overall safety profile between the groups receiving UB-312 and placebo. Subsequent vaccinations did not result in an increase in local vaccination-site reactions, nor were there any severe local reactions (as observed in the past with other active immunotherapies targeting α-Syn19) [11].

4. Conclusion

This review has presented the current treatment options for Parkinson's Disease, the mechanism of designing a therapeutic vaccine for PD, and the most up-to-date and effective therapeutic vaccine, which is UB-312. Targeting forms of α-synuclein, which are associated with PD, have been found to be the major way of designing the vaccine. Currently, among the therapeutic vaccines, UB-312 has been proven to be the best in both safety and immunogenicity as evidenced in the clinical trial. In the future, clinical trials with larger scales could be conducted to further prove UB-312's safety and immunogenicity. The success of UB-312 in the clinical trial suggests a promising future for therapeutic vaccines in PD treatment.

References

[1] Beitz J M. Parkinson's disease: a review. Frontiers in Bioscience-Scholar, 2014, S6(1): 65–74.

[2] Parkinson's Foundation. Parkinson's Foundation. /2024-03-22. https://www.parkinson.org/.

[3] Reich S G, Savitt J M. Parkinson's Disease. Medical Clinics of North America, 2019, 103(2): 337–350.

[4] Matarazzo M, Perez-Soriano A, Stoessl A J. Dyskinesias and levodopa therapy: why wait?. J Neural Transm, 2018, 125(8): 1119–1130.

[5] Sharma V D, Patel M, Miocinovic S. Surgical Treatment of Parkinson's Disease: Devices and Lesion Approaches. Neurotherapeutics, 2020, 17(4): 1525–1538.

[6] Mak M K, Wong-Yu I S, Shen X, et al. Long-term effects of exercise and physical therapy in people with Parkinson disease. Nat Rev Neurol, 2017, 13(11): 689–703.

[7] Liu T, Lao L. Tai Chi for Patients with Parkinson's Disease. 2012-05-01/2024-03-11. https://www.nejm.org/doi/full/10.1056/NEJMc1202921.

[8] Parkinson's Disease: Challenges, Progress, And Promise. National Institute Of Neurological Disorders And Stroke. /2024-03-11.

[9] Dehay B, Bourdenx M, Gorry P, et al. Targeting α-synuclein for treatment of Parkinson's disease: mechanistic and therapeutic considerations. The Lancet Neurology, 2015, 14(8): 855–866.

[10] Polymeropoulos M H, Lavedan C, Leroy E, et al. Mutation in the α-Synuclein Gene Identified in Families with Parkinson's Disease. Science, 1997, 276(5321): 2045–2047.

[11] Yu H J, Thijssen E, van Brummelen E, et al. A Randomized First-in-Human Study With UB-312, a UBITh® α-Synuclein Peptide Vaccine. Movement Disorders, 2022, 37(7): 1416–1424.

[12] Nimmo J T, Verma A, Dodart J-C, et al. Novel antibodies detect additional α-synuclein pathology in synucleinopathies: potential development for immunotherapy. Alz Res Therapy, 2020, 12(1).