The Potential of Therapeutic Vaccines and Antibodies against Parkinson's Disease

Mengyu Gu *

School of Life Science and Technology, China Pharmaceutical University, Nanjing, Jiangsu Province, China

* Corresponding Author Email: gumengyu@stu.cpu.edu.cn

Abstract: Parkinson's disease is the second largest neurodegenerative disease after Alzheimer's disease. There are about 6.3 million Parkinson's patients worldwide. With the worldwide trend of population aging, increasingly elderly people will face the risk of suffering from Parkinson's disease. However, the existing drugs can only alleviate the symptoms to some extent and are often accompanied by drug resistance and serious side effects, so more effective treatment methods are needed. In recent years, scientists have realized the immense potential of immunotherapy for neurodegenerative diseases. More studies about vaccines and monoclonal antibodies for Parkinson's disease have been reported, and the results are worthy of discussion and consideration. This paper summarizes two preclinical studies on prophylactic vaccines and three clinical trials on monoclonal antibodies against Parkinson's disease, with a discussion about their advantages and disadvantages. Additionally, this paper summarizes the two main challenges of the application of immunotherapy in Parkinson's disease, which are how to reduce the adverse effects and how to ensure the macromolecules penetrate the blood-brain barrier.

Keywords: Parkinson’s disease; alpha-synuclein; vaccines; monoclonal antibodies.

1. Introduction

Parkinson's disease (PD) is a type of neurodegenerative disease related to the damage of nigra-striatal pathway and the progressive loss of dopaminergic neurons in the brain. The main symptoms of PD are motor disorders including resting tremor, muscle rigidity, motor retardation, and gait disturbance. Besides, patients may also suffer from non-motor disorders such as cognitive dysfunction, sleep, and sensory abnormalities. Since James Parkinson first reported PD in the past two hundred years, doctors, scientists, and patients have made unremitting efforts to defeat it. From drug treatment, surgical treatment to exercise rehabilitation training, people continue to explore ways to fight against this kind of disease. However, it is still difficult to reverse or stop the progress of PD. With the aging of the population and the prolongation of life expectancy, PD has become the fastest-growing neurodegenerative disease. It is estimated that there will be more than 12 million PD patients in the world by 2040 [1].

At present, the pathogenesis of PD remains obscure. It is believed that only five percent of PD is triggered by genetic factors, and most PD cases are still idiopathic. The related factors comprise heavy metals, pesticides, traumatic injuries and pathogenic microorganism infection. The research on the pathogenesis of PD is mainly focused on α-synuclein (α-syn), apoptosis, mitochondrial dysfunction, oxidative stress and neuroinflammation. These mechanisms are interdependent and can lead to the occurrence of PD all together. When the removal rate of α-syn is less than the generation rate, the Lewy bodies, which are mainly composed of α-syn oligomers, are gradually formed in the brain, and could be regarded as a pathological PD marker. Therefore, the anomalous aggregated α-syn is the critical cause of PD. As one of the pathways of programmed cell death, apoptosis can be activated by a variety of biological signals. Under the action of apoptosis stimulating factor, the permeableness of mitochondrial external membrane is increased, Cytochrome C is released, and the cascade of apoptotic proteases is triggered. Consequently, these events eventually lead to neuronal apoptosis. Mitochondrial dysfunction can damage glial cells and neurons, resulting in the decrease of adenosine triphosphate, the increase of free radicals, the imbalance of calcium homeostasis and the production

of a variety of abnormal proteins, resulting in neurodegeneration. Oxidative stress is also the focus of research on the pathogenesis of PD. When the content of reactive oxygen species increases in the brain, oxidative stress will be induced, and brain tissue will be damaged. Under normal circumstances, microglia and astrocytes sustain the dynamic balance of the central nervous system by clearing synaptic glutamate and releasing neurotrophic factors. However, when these glial cells are activated by secretory factors of damaged neurons, they can cause neuronal inflammation and neuronal degeneration, which may promote the development of PD [2].

The existing drugs against PD are mainly aimed at increasing the relative content of dopamine in the brain, such as levodopa, COMT inhibitors and dopamine receptor agonists. Levodopa is the credible standard in the treatment of PD, but its half-life in the blood is truly short, which will lead to large fluctuations in blood concentration in a short period of time, making patients get fatigued. However, with the progress of equipment, formulation and technology, people gradually overcome their defects. Compound preparations such as levodopa/carbidopa gel have been introduced to the public. COMT inhibitors, represented by entacapone, increase their bioavailability by inhibiting the metabolism of levodopa. Monoamine oxidase B inhibitors, represented by selegiline, have been used as primary therapeutic drugs for PD in Japan. In addition to improving motor symptoms, it can also reduce the dose of levodopa needed by patients and may have neuroprotective effects. Dopamine receptor agonists mainly stimulate dopamine D2 receptor. Its half-life is longer than levodopa, and the probability to develop motor complications after preliminary treatment is lower, so dopamine agonists can be used to deal with patients' fatigue. Other drugs against PD include adenosine A2A receptor inhibitors and amantadine sustained release preparations [3]. In addition to drug therapy, surgical treatment including pallidotomy and deep brain stimulation were once popular for some time [4]. Even sports rehabilitation training is also added to the treatment of PD [5], but there is still no effective way to cure the disease. The limitations include drug resistance, serious adverse reactions, and poor compliance. Therefore, it is of important research value to explore different methods.

Recently, scientists have pay great attention to immunotherapy for neurodegenerative diseases. There are twenty vaccine research and development pipelines for Alzheimer's disease worldwide, and tertomotide has already been put on the market. As one of the neurodegenerative diseases, PD may also be treated through immunotherapy. As a marker most closely related to the pathogenesis of PD, α-syn can be regarded as a target for the design of vaccines and antibody medicine. This paper summarizes two prophylactic vaccines against PD and three monoclonal antibodies that have entered clinical trials. The mechanism, safety and effectiveness of their function are described. At the same time, their advantages and disadvantages are discussed.

2. Vaccines Against PD

2.1. An α-syn/Grp94-based vaccine reshapes the peripheral immune environment of the chronic PD model and inhibits the proliferation of microglia

Cintia Roodveldt's team designed a vaccine based on α-syn /Grp94 proteins (1:1) to immunize mice and then used 1-murmethylmurine 4-tetrahydropyridine (MPTP) to develop PD mouse models [6]. They found that the vaccine improved the PD pathology and inhibited persistent microglial proliferation, which is a recognized neuropathological feature of PD. The mice were either directly immunized or inoculated by adoptive transfer of splenocytes isolated from donor mice, both vaccination methods were assessed. Then behavioral tests were conducted to evaluate their motor abilities and immunological analyses were carried out.

Through detecting the levels of Immunoglobulin G (IgG) molecules and inflammatory factors, the results showed that the two immunization methods can both make the immune system of mice produce sufficient responses, including humoral immunity and cellular immunity. In addition, the vaccine alleviated the PD-related neuroinflammatory response, especially significantly inhibited the activation and proliferation of microglia. In addition, the vaccine promoted the transformation of PD-related peripheral immune cells to Th1 and Th2 phenotypes, maintaining immune dynamic balance.

This is the first time that α-syn was used as a vaccine to immunize mice. Although the results of the study on whether the vaccine can directly reduce the aggregation of α-syn in the brain of mice has not been reported, it provided a foundation for later research.

2.2. A novel vaccine based on α-syn peptide epitope showed immunization effects on the PD model

Myeong Ok Kim's team designed and identified a peptide epitope vaccine based on α-syn by using computer models and bioinformatics analysis techniques [7]. They also coupled the vaccine with immunogenic carrier protein (KLH or OVA) to improve the immunogenicity of the vaccine. After immunizing the mice, they established the PD model by injecting α-syn directly into the ventricle of the mice.

The results of behavioral experiments showed that the motor function of vaccinated PD mice, especially those vaccinated with carrier protein vaccine, was significantly improved. Besides, the level of α-syn decreased and the level of dopamine related markers increased. In addition, IgG levels in spleen and plasma of vaccinated PD mice increased, while plasma levels of interleukin-10 (IL-10) decreased, indicating that the vaccine can effectively activate the immune system and promote antibody production. Finally, they found that the vaccine relieved nerve inflammation by reducing the activation of microglia, astrocytes and proinflammatory cytokines. These results suggest that immunization with α-syn vaccine, especially the α-syn vaccine coupled with immunogenic carrier protein, can effectively reduce the quantity of α-syn aggregates in the mice' brain and alleviate the pathology and symptoms associated with PD.

This study proved the efficacy of the vaccine from different aspects and preliminarily proved that it was non-toxic. However, there is a lack of experiments at the cellular level for further verification. In short, when developing effective anti-PD immunotherapy, it is necessary to use correct T cell subsets and screen appropriate α-syn epitopes as targets. It is worth noting that currently there is no therapeutic vaccines against PD, which can be a novel strategy to treat PD.

Apart from active immunity, passive immunotherapy strategy, includes the α-syn-targeted monoclonal antibodies, can function more promptly to clear α-syn aggregates, which will be discussed below.

3. Monoclonal antibodies against PD

3.1. Prasinezumab (PRX002/RG7935)

Jointly developed by Prothena and Roche, Prasinezumab is a humanized monoclonal antibody targeting α-syn aggregation in patients with idiopathic PD. During 2014 to 2016, several research centers in the United States carried out a phase 1b clinical trial [8] to evaluate the safety and tolerance of Prasinezumab. Eighty subjects between the ages of 40 and 80 were randomly assigned to receive six different doses of Prasinezumab (0.3mg/kg, 1.0mg/kg, 3.0mg/kg, 10mg/kg, 30mg/kg, 60mg/kg) or placebo. All subjects received a specified dose of intravenous injection 3 times every 28 days.

The results showed that Prasinezumab is generally safe and well tolerated, with no serious adverse events associated with it. The common adverse reactions include constipation, peripheral edema, lumbar puncture syndrome and upper respiratory tract infection. It is also found that Prasinezumab exposure increased in a dose-proportional manner, consistent with dose-exposure-effect. In addition, Prasinezumab does not bind to healthy brain tissue, indicating that it has the specificity of targeting lesions. Moreover, Prasinezumab has been proved to effectively reduce the level of free α-syn in serum, and the highest dose was observed to decrease by as much as 97% after a single injection. The above results indicate that Prasinezumab has a high possibility of treating PD.

It is worth noting that most of the subjects in the clinical trial were white people (97.5%) and male (80%), with fewer female subjects. Although the incidence of PD in women is lower than that in men, the pathogenesis is faster and the mortality is higher, so it is necessary to explore more detailed effects of Prasinezumab on female subjects.

Later in 2017, a phase II clinical trial [9] initiated in the US and Europe were carried out to verify the efficacy of Prasinezumab. The 316 PD patients participated in the trial were recruited from 57 regions and were allowed to take monoamine oxidase B inhibitors during the trial.

The subjects were randomly assigned to receive two different doses of Prasinezumab (1500mg or 4500mg) or placebo. All of them received a specified dose of intravenous injection every 4 weeks. Furthermore, the subjects who received the placebo were then divided into two groups to receive Prasinezumab treatment (1500mg or 4500mg). The results suggested that there was no significant discrepancy in MDS Unified-Parkinson Disease Rating Scale (MDS-UPDRS) scores relative to the baseline of the treatment group compared with the placebo group. Besides, there were no significant differences in other evaluation indexes among the groups, including changes in dopamine transporter levels and the safety and pharmacokinetic indicators. Although the results were not perfect, this clinical trial played an important role in the field of immunotherapy of PD.

3.2. Cinpanemab (BIIB054)

Cinpanemab is a humanized monoclonal antibody targeting α-syn, and its affinity for α-syn aggregates is 800 times higher than that of monomers. A phase II clinical trial [10] assessed the protective effects of Cinpanemab against PD.

A total of 357 subjects were recruited in the trial. They were randomly assigned to receive three different doses of Cinpanemab (250 mg, 1250 mg, or 3500 mg) or placebo. All subjects received a treatment every month for a year. The main evaluation index was the alterationof the total score of MDS-UPDRS relative to the baseline at 52 and 72 weeks, respectively. Other evaluation indexes included the level of dopamine transporter and the safety and tolerance of Cinpanemab. The results showed that Cinpanemab was safe and highly tolerable. Nevertheless, the similarity of the MDS-UPDRS score and other molecular-level evaluation outcome suggested that Cinpanemab did not significantly slow down the progression of PD. Therefore, it has been stopped to continue development.

3.3. MEDI1341

MEDI1341 is a high affinity monoclonal antibody against monomer and aggregating α-syn, originally developed by AstraZeneca. At present, it is still in phase I clinical trial.

The preclinical study [11] conducted before 2019 found that MEDI1341 could block the transmission of α-syn between cells in vitro. In PD rats and Macaca fascicularis models, 0.4% of MEDI1341 could permeate the blood-brain barrier (BBB) into the central nervous system and reduce the level of α-syn in cerebrospinal fluid and interstitial fluid. In addition, MEDI1341 treatment significantly reduced the aggregation and transmission of α-syn along axons in mice.

According to the study, the Macaca fascicularis were divided into four groups and injected intravenously with different doses of MEDI1341 (0 mg/kg, 25 mg/kg, 75 mg/kg, 150 mg/kg) once a week for 13 weeks. On the third day after the last administration, cerebrospinal fluid was collected from the animals and α-syn levels were tested. The results suggested that MEDI1341 significantly reduced the level of bound α-syn, but could not reduce the level of free α-syn.

In addition, the existence of red blood cells would lead to the higher detection value than the real value, since the blood contamination in cerebrospinal fluid samples significantly affects the measurement of dissociativeα-syn. This study avoided this kind of interference to the experimental results by full centrifugation and other operations.

In short, this study preliminarily proved the efficacy of MEDI1341 for the treatment of PD, but how to improve the efficiency of macromolecular antibody drugs to penetrate the BBB is still a thorny problem. Two possible methods about it have been reported. The first method is to use the transferrin receptor (TfR), which has been reported by Roche company to transfer antibodies into the brain to treat Alzheimer's disease. However, since TfR exists in many other parts of the human body, there is no guarantee that it will only be transferred into the brain without affecting other organs or tissues. Another method is to use ultrasound to temporarily open the BBB. The ultrasound can generate

mechanical waves and exert mechanical stress on the blood vessel wall, resulting in stretching and opening of tight junctions between endothelial cells. The BBB can automatically heal spontaneously within hours. Studies on Alzheimer's disease have proved the safety and efficacy of this method in clinical trials.

4. Conclusion

This paper summarizes the reported results of two prophylactic vaccine studies and three monoclonal antibody studies in clinical trials, all of which are targeting α-syn to treat PD. Compared with chemical drugs, active immunotherapy and passive immunotherapy have the advantages of long-term effectiveness and rapid effect, respectively. However, the adverse effects of immunotherapy such as serious anemia and dysphagia should not be neglected. Additionally, due to the obstruction of the BBB, both vaccines and antibodies face the same difficulty, which is how to deliver the macromolecules into the nervous system.

In the past two decades, immunotherapy has been applied to the treatment of plenty of diseases, especially in the treatment of cancer. Despite the existence of challenges and obstacles, the development of vaccines and antibodies against PD is never stopped and has brought promising results. Hopefully, immunotherapy is a potential strategy and can bring breakthrough success to the treatment of PD.

References

[1] Warnecke T, Lummer C, Rey JW, et al. Parkinson's disease. Inn Med (Heidelb), 2023, 64(2): 131-138.

[2] Morris HR, Spillantini MG, Sue CM, et al. The pathogenesis of Parkinson's disease. Lancet, 2024, 403(10423): 293-304.

[3] Murakami H, Shiraishi T, Umehara T, et al. Recent Advances in Drug Therapy for Parkinson's Disease. Intern Med, 2023, 62(1): 33-42.

[4] Lo Buono V, Lucà Trombetta M, Palmeri R, et al. Subthalamic nucleus deep brain stimulation and impulsivity in Parkinson's disease: a descriptive review. Acta Neurol Belg, 2021, 121(4): 837-847.

[5] Feng YS, Yang SD, Tan ZX, et al. The benefits and mechanisms of exercise training for Parkinson's disease. Life Sci, 2020, 245: 117345.

[6] Villadiego J, Labrador-Garrido A, Franco JM, et al. Immunization with α-synuclein/Grp94 reshapes peripheral immunity and suppresses microgliosis in a chronic Parkinsonism model. Glia, 2018, 66(1): 191-205.

[7] Park JS, Ahmad R, Choe K, et al. Immunization Effects of a Novel α-Synuclein-Based Peptide Epitope Vaccine in Parkinson's Disease-Associated Pathology. Vaccines (Basel), 2023, 11(12): 1820.

[8] Jankovic J, Goodman I, Safirstein B, et al. Safety and Tolerability of Multiple Ascending Doses of PRX002/RG7935, an Anti-α-Synuclein Monoclonal Antibody, in Patients With Parkinson Disease: A Randomized Clinical Trial. JAMA Neurol, 2018, 75(10): 1206-1214.

[9] Pagano G, Taylor KI, Anzures-Cabrera J, et al. Trial of Prasinezumab in Early-Stage Parkinson's Disease. N Engl J Med, 2022, 387(5): 421-432.

[10] Lang AE, Siderowf AD, Macklin EA, et al. Trial of Cinpanemab in Early Parkinson's Disease. N Engl J Med, 2022, 387(5): 408-420.

[11] Schofield DJ, Irving L, Calo L, et al. Preclinical development of a high affinity α-synuclein antibody, MEDI1341, that can enter the brain, sequester extracellular α-synuclein and attenuate α-synuclein spreading in vivo. Neurobiol Dis, 2019, 132: 104582.