

# Immunotherapies Targeting $\alpha$ -Synuclein in Parkinson Disease

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**Background:** Parkinson disease (PD) is a progressive neurodegenerative disorder. Pathologic diagnosis of PD relies on loss of dopamine neurons in the substantia nigra and accumulation of the abnormal protein  $\alpha$ -synuclein in the form of Lewy bodies and Lewy neurites. Alteration in aggregation properties of this protein is believed to play a central role in the pathogenesis of PD.

**Observations:** Huge interest has developed in antibody-based therapies for PD. Several studies have tested immunotherapies in PD animal models with the aim of targeting

$\alpha$ -synuclein. Immunotherapies can be instituted in 2 ways: active immunization in which the immune system is stimulated to produce antibodies against  $\alpha$ -synuclein or passive immunization in which antibodies against  $\alpha$ -synuclein are directly administered.

**Conclusions:** Immunotherapy against  $\alpha$ -synuclein has provided a new therapeutic avenue in neuroprotection. Results from the first human clinical trial are promising, but despite these results, more work is needed to clarify the role of  $\alpha$ -synuclein in the pathogenesis of PD in humans.

Parkinson disease (PD) is a progressive neurodegenerative disorder, characterized by diverse clinical symptoms. PD can present with rest tremor, bradykinesia, rigidity, falls, postural instability, and multiple nonmotor symptoms. Marras and colleagues estimated in a comprehensive meta-analysis that there were 680,000 individuals with PD in the US in 2010; this number is expected to double by 2030 based on the US Census Bureau population projections.<sup>1</sup> An estimated 110,000 veterans may be affected by PD; hence, understanding of PD pathology, clinical progression, and effective treatment strategies is of paramount importance to the Veterans Health Administration (VHA).<sup>2</sup>

The exact pathogenesis underlying clinical features is still being studied. Pathologic diagnosis of PD relies on loss of dopamine neurons in the substantia nigra and accumulation of the abnormal protein,  $\alpha$ -synuclein, in the form of Lewy bodies and Lewy neurites. Lewy bodies and neurites accumulate predominantly in the substantia nigra in addition to other brain stem nuclei and cerebral cortex. Lewy bodies are intraneuronal inclusions with a hyaline core and a pale peripheral halo. Central core stains positive for  $\alpha$ -synuclein.<sup>3,4</sup> Lewy neurites are widespread and are believed to play a larger role in the pathogenesis of PD compared with those of Lewy bodies.<sup>5</sup>

## $\alpha$ -SYNUCLEIN

$\alpha$ -synuclein is a small 140 amino-acid protein with a N-terminal region that can in-

teract with cell membranes and a highly acidic unstructured C-terminal region.<sup>6</sup>  $\alpha$ -synuclein is physiologically present in the presynaptic terminals of neurons and involved in synaptic plasticity and vesicle trafficking.<sup>7</sup> There are different hypotheses about the native structure of  $\alpha$ -synuclein. The first suggests that it exists in tetrameric form and may be broken down to monomer, which is the pathogenic form of  $\alpha$ -synuclein. The second hypothesis suggests that it exists primarily in monomeric form, whereas other studies have shown that both forms exist and with pathologic changes, monomer accumulates in abundance and is neurotoxic.<sup>8-11</sup> Work by Burré and colleagues shows that native  $\alpha$ -synuclein exists in 2 forms: a soluble, cytosolic  $\alpha$ -synuclein, which is monomeric, and a membrane-bound multimeric form.<sup>12,13</sup>

Alteration in aggregation properties of this protein is believed to play a central role in the pathogenesis of PD.<sup>14,15</sup> Pathologic  $\alpha$ -synuclein exists in insoluble forms that can aggregate into oligomers and fibrillar structures.<sup>16</sup> Lysosomal dysfunction may promote accumulation of insoluble  $\alpha$ -synuclein. Prior work has shown that several degradation pathways in lysosomes, including the ubiquitin-proteasome system and autophagy-lysosomal pathway, are down regulated, thus contributing to the accumulation of abnormal  $\alpha$ -synuclein.<sup>17,18</sup> Accumulation of pathologic  $\alpha$ -synuclein leads to mitochondrial dysfunction in PD

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*Fed Pract.* 2020;37(8):375-379.  
doi:10.12788/fp.0026

animal models, contributing further to neurotoxicity.<sup>19,20</sup> Aggregates of phosphorylated  $\alpha$ -synuclein have been demonstrated in dementia with Lewy body.<sup>21</sup>

In addition,  $\alpha$ -synuclein aggregates may be released into extracellular spaces to be taken up by adjacent cells, where they can cause further misfolding and aggregation of protein.<sup>22</sup> Previous work in animal models suggested a prion proteinlike spread of  $\alpha$ -synuclein.<sup>23</sup> This finding can have long-term therapeutic implications, as preventing extracellular release of abnormal form of  $\alpha$ -synuclein will prevent the spread of pathologic protein. This can form the basis of neuroprotection in patients with PD.<sup>24</sup>

It has been proposed that  $\alpha$ -synuclein accumulation and extracellular release initiates an immune response that leads to activation of microglia. This has been shown in PD animal models, overexpressing  $\alpha$ -synuclein. In 2008 Park and colleagues demonstrated that microglial activation is enhanced by monomeric  $\alpha$ -synuclein, not by the aggregated variant.<sup>25</sup> Other studies have reported activated microglia around dopaminergic cells in substantia nigra.<sup>26</sup> Sulzer and colleagues showed that peptides from  $\alpha$ -synuclein can act as antigens and trigger an autoimmune reaction via T cells.<sup>27</sup> PD may be associated with certain HLA-haplotypes.<sup>28</sup> In other words,  $\alpha$ -synuclein can induce neurodegeneration via different mechanisms, including alteration in synaptic vesicle transmission, mitochondrial dysfunction, neuroinflammation, and induction of humoral immunity.

### Immunization

Due to these observations, there had been huge interest in developing antibody-based therapies for PD. A similar approach had been tested in Alzheimer disease (AD). Intracellular tangles of tau protein and extracellular aggregates of amyloid are the pathologic substrates in AD. Clinical trials utilizing antibodies targeting amyloid showed reduction in abnormal protein accumulation but no significant improvement in cognition.<sup>29</sup> In addition, adverse events (AEs), such as vasogenic edema and intracerebral hemorrhage, were reported.<sup>30</sup> Careful analysis of the data suggested that inadequate patient selection or targeting

only amyloid, may have contributed to unfavorable results.<sup>31</sup> Since then, more recent clinical trials have focused on careful patient selection, use of second generation anti-amyloid antibodies and immunotherapies targeting tau.<sup>32</sup>

Several studies have tested immunotherapies in PD animal models with the aim of targeting  $\alpha$ -synuclein. Immunotherapies can be instituted in 2 ways: active immunization in which the immune system is stimulated to produce antibodies against  $\alpha$ -synuclein or passive immunization in which antibodies against  $\alpha$ -synuclein are administered directly. Once  $\alpha$ -synuclein antibodies have crossed the blood-brain barrier, they are hypothesized to clear the existing  $\alpha$ -synuclein. Animal studies have demonstrated the presence of these antibodies within the neurons. The mechanism of entry is unknown. Once inside the cells, the antibodies activate the lysosomal clearance, affecting intracellular accumulation of  $\alpha$ -synuclein. Extracellularly, they can bind to receptors on scavenger cells, mainly microglia, activating them to facilitate uptake of extracellular  $\alpha$ -synuclein. Binding of the antibodies to  $\alpha$ -synuclein directly prevents the uptake of toxic protein by the cells, blocking the transfer and spread of PD pathology.<sup>33</sup>

### Active Immunization

Active immunization against  $\alpha$ -synuclein was demonstrated by Masliah and colleagues almost a decade ago. They administered recombinant human  $\alpha$ -synuclein in transgenic mice expressing  $\alpha$ -synuclein under the control of platelet-derived growth factor  $\beta$ . Reduction of accumulated  $\alpha$ -synuclein in neurons with mild microglia activation was noted. It was proposed that the antibodies produced were able to bind to abnormal  $\alpha$ -synuclein, were recognized by the lysosomal pathways, and degraded.<sup>34</sup> Ghochikyan and colleagues developed vaccines by using  $\alpha$ -synuclein-derived peptides. This induced formation of antibodies against  $\alpha$ -synuclein in Lewy-bodies and neurites.<sup>35</sup> Over time, other animal studies have been able to expand on these results.<sup>36</sup>

AFFiRiS, an Austrian biotechnology company, has developed 2 peptide vaccines PD01A and PD03A. Both peptides when administered to PD animal models caused

antibody-based immune response against aggregated  $\alpha$ -synuclein. Humoral autoimmune response was not observed in these studies; no neuroinflammation or neurotoxicity was noted. These peptides did not affect levels of physiologic  $\alpha$ -synuclein, targeting only the aggregated form.<sup>37</sup> These animal models showed improved motor and cognitive function. Similar results were noted in multiple system atrophy (MSA) animal models.<sup>38,39</sup>

The first human phase 1, randomized, parallel-group, single-center study recruited 32 subjects with early PD. Twelve subjects each were included in low- or high-dose treatment group, and 8 were included in the control group. Test subjects randomly received 4 vaccinations of low- or high-dose PD01A. Both doses were well tolerated, and no drug-related serious AEs were reported. The study confirmed the tolerability and safety of subcutaneous PD01A vaccine administration. These subjects were included in a 12-month, phase 1b follow-up extension study, AFF008E. In 2018, it was reported that administration of 6 doses of PD01A, 4 primary and 2 booster immunization, was safe. The vaccine showed a clear immune response against the peptide and cross-reactivity against  $\alpha$ -synuclein targeted epitope. Booster doses stabilized the antibody titers. Significant increase in antibody titers against PD01A was seen over time, which was translated into a humoral immune response against  $\alpha$ -synuclein. In addition, PD01A antibodies also were reported in cerebrospinal fluid.<sup>40</sup>

AFFiRiS presented results of a phase 1 randomized, placebo-controlled trial in 2017, confirming the safety of PD03A in patients with PD. The study showed a clear dose-dependent immune response against the peptide and cross-reactivity against  $\alpha$ -synuclein targeted epitope.<sup>41</sup> AFFiRiS recently presented results of another phase 1 clinical study assessing the safety and tolerability of vaccines PD01A and PD03A in patients with early MSA. Both vaccines were well tolerated, and PD01A induced an immune response against the peptide and  $\alpha$ -synuclein epitope.<sup>42</sup> These results have provided hope for further endeavors to develop active immunization strategies for PD.

### Passive Immunization

Passive immunization against  $\alpha$ -synuclein was first reported by Masliah and colleagues in 2011. A monoclonal antibody against the C-terminus of  $\alpha$ -synuclein, 9E4, was injected into a transgenic mouse model of PD. There was reduction in  $\alpha$ -synuclein aggregates in the brain along with improvement in motor and cognitive impairment.<sup>43</sup> The C-terminus of  $\alpha$ -synuclein plays a key role in the pathogenesis of PD. Changes in the C-terminus of  $\alpha$ -synuclein induces formation of  $\alpha$ -synuclein oligomers and subsequent neuronal spread. Antibody binds to the C-terminus and prevents structural changes that can lead to oligomerization of  $\alpha$ -synuclein. Since the first study by Masliah, few other immunization studies utilized different antibodies against the C-terminus of  $\alpha$ -synuclein. It was shown in a mouse model that binding of such antibodies promoted clearance of the  $\alpha$ -synuclein by microglia.<sup>44</sup>

Based on these animal studies, Prothena Biosciences (South San Francisco, CA) designed a phase 1, double-blind, randomized, placebo-controlled clinical trial of prasinezumab (investigational monoclonal antibody against C-terminus of  $\alpha$ -synuclein), in subjects without PD. The results showed that it was well tolerated, and there was dose-dependent reduction in the levels of free  $\alpha$ -synuclein in plasma.<sup>45</sup> A 6-month phase 1b trial to evaluate the safety, tolerability and immune system response to multiple ascending doses of prasinezumab via IV infusion once every 28 days was conducted in 64 patients with PD. The drug was found to be safe, and levels of free serum  $\alpha$ -synuclein were reduced up to 97%.<sup>46</sup> Roche (Basel, Switzerland) and Prothena are conducting a multicenter, randomized, double-blind phase 2 trial in patients with early PD to evaluate the efficacy of prasinezumab vs placebo.<sup>47</sup>

BIIB054 is another monoclonal antibody that targets the N-terminal of  $\alpha$ -synuclein. In animal models, antibodies targeting the N-terminus reduced  $\alpha$ -synuclein triggered cell death and reduced the number of activated microglia.<sup>48</sup> BIIB054, from Biogen (Cambridge, MA), was studied in 40 healthy subjects and was well tolerated with a favorable safety profile and could cross the blood-brain barrier. Like the prasinezumab study,

this also was an ascending-dose study to assess safety and tolerability. In 2018, a randomized, double-blind, placebo-controlled, single-ascending dose study in patients with PD reported that BIIB054 was well tolerated, and the presence of BIIB054-synuclein complexes in the plasma were confirmed.<sup>49</sup> A phase 2, multicenter, randomized, double-blind, placebo-controlled study (SPARK) with an active-treatment dose-blinded period, designed to evaluate the safety, pharmacokinetics, and the pharmacodynamics of BIIB054 is currently recruiting patients with PD.

Finally, BioArctic (Stockholm, Sweden) developed antibodies that are selective for oligomeric forms of  $\alpha$ -synuclein, which it licensed to AbbVie (North Chicago, IL).<sup>50</sup> These antibodies do not target the N- or C-terminus of  $\alpha$ -synuclein. Since  $\alpha$ -synuclein oligomers play an important role in the pathogenesis of PD, targeting them with antibodies at an early stage may prove to be an effective strategy for removal of pathogenic  $\alpha$ -synuclein. Clinical trials are forthcoming.

## CONCLUSIONS

Immunotherapy against  $\alpha$ -synuclein has provided a new therapeutic avenue in the field of neuroprotection. Results from the first human clinical trial are promising, but despite these results, more work is needed to clarify the role of  $\alpha$ -synuclein in the pathogenesis of PD in humans. Most of the work concerning  $\alpha$ -synuclein aggregation and propagation has been reported in animal models. Whether similar process exists in humans is a debatable question. Similarly, more knowledge is needed about how and where in the human brain antibodies act to give neuroprotective effects. Timing of administration of immunotherapies in real time will be a crucial question.

PD is clinically evident once 80% of dopaminergic neurons in substantia nigra are lost due to neurodegeneration. Should immunotherapy be administered to symptomatic patients with PD, or if it will be beneficial only for presymptomatic, high-risk patients needs to be determined. Like AD trials, not only careful selection of patients, but determination of optimal timing for treatment will be essential. As the understanding of PD pathogenesis and therapeutics evolves, it will be-

come clear whether immunization targeting  $\alpha$ -synuclein will modify disease progression.

## Author Disclosures

The author reports no actual or potential conflicts of interest with regard to this article.

## Disclaimer

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