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Alpha-Synuclein Targeting Monoclonal Antibody Therapy Treatment for Parkinson's Disease

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ABSTRACT

An investigation was done on plausible antibody treatments for alpha-synuclein, which is an instigator for the dopamine-lacking neurodegenerative disease Parkinson's to occur in patients due to its aggregation. Trials working towards slowing the pathogenesis of Parkinson's Disease through monoclonal antibodies for alpha-synuclein were analyzed. Previously, similar therapies were done in other neurodegenerative diseases like Alzheimer's, allowing for a hopeful hypothesis in Parkinson's. Active and Passive antibody treatments were compared and discussed: Pranizeumab, Cipanemab, PD01A, and UB-312. Trials often found success in animal models and not the same outcome in humans within the passive studies. In active studies, however, more hopeful results were presented, showing built immunity towards alpha-synuclein and enhancement of motor symptoms. Though some studies led to a dead end, studies use information to complete future phases. Monoclonal antibody treatment for Parkinson's Disease is a real future in the fight for reducing the pathogenesis of Parkinson's Disease.

Background

Parkinson's Disease

Parkinson's is a neurodegenerative disorder attacking the mobility of an individual. It progressively worsens and is typically prevalent during old age, as the average age for a Parkinson's diagnosis is 60 years of age (Johns Hopkins Medicine, nd). Younger findings of Parkinson's disease are considered to be in their subset, being called Young-Onset Parkinson's Disease. In the United States, around 500,000 people have been diagnosed with Parkinson's Disease.

Biologically, the neurodegenerative nature of the disease causes the loss of nerve cells within the brain. This loss occurs in the section of the brain referred to as the Substantia Nigra (refer to Fig.1), which holds nerve cells made to transmit dopamine through the body. Dopamine is a neurotransmitter crucial in sending messages to other parts of the body to follow through with its movement.

Parkinson's comes with a variety of life-altering symptoms and effects. Most commonly, patients see tremors occurring or slowness during movement. In the later stages of the disease, victims are said to have limited to no movement without assistance and have severe stiffness throughout the limbs of the body.

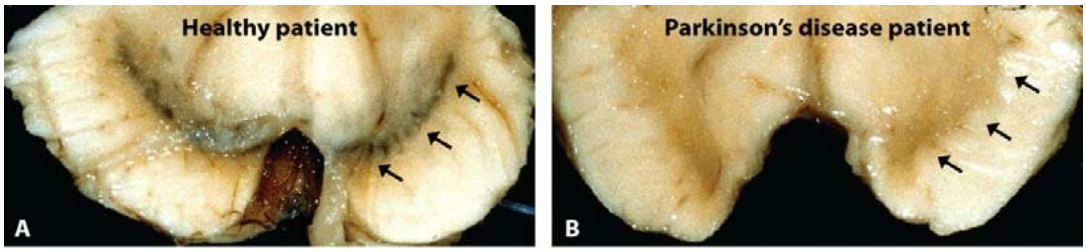

Figure 1. Substantia Nigra of patients without Parkinson's present in comparison to a patient with the disease. (Aron, 2006)

Lewy Bodies

In Parkinson's Disease and Lewy Body Dementia, there is a presence of abnormal clumps of protein in the brain's nerve cells called Lewy Bodies (refer to Fig. 2). The protein found in these Lewy Bodies is known as alpha-synuclein. The abruptions these deposits create within the brain cause the neurotransmitters and chemicals to halt. Because of this, Lewy bodies are caused by the motor side effects of Parkinson's disease.

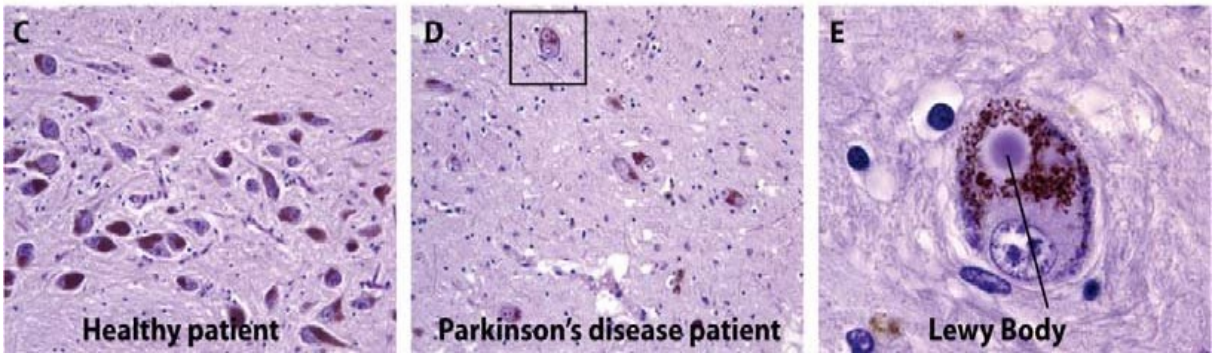

Figure 2. Nerve cells in a healthy patient without Parkinson's Disease, versus the accumulation of a Lewy Body in someone who has Parkinson's (Aron, 2006).

Alpha-Synuclein

Within the Lewy Bodies present in the brain, there is a protein with aggregation and abnormal folds called alpha-synuclein. Alpha-synuclein is referred to as a "presynaptic neuronal protein" which has direct ties to Parkinson's in its neurological and genetic aspects. It is described that alpha-synuclein contains toxic components like "soluble oligomeric conformations and termed protofibrils" which are the causes for the chaos ensuing which ends in nerve cell apoptosis (Stefanis, 2012). The oligomers bind with VAMP 2 and disrupt the SNARE protein complexes formations and dopamine release, a lack in patients with Parkinson's (Wang & Krainc 2021).

Typically, alpha-synuclein controls the release of neurotransmitters and is abundant in the brain. Alpha-synuclein makes up 1% of the proteins present within the neuron. When the folds of the protein occur improperly it can cause negative effects and create Lewy Bodies affecting Parkinson's.

Genetic mutation of the alpha-synuclein protein can also be an issue creating a higher risk of Parkinson's. Some locations on the alpha-synuclein gene that have been discovered to have mutations are A53T, A30P, E46K, H50Q, and G51D.

Recently, new investigations into Parkinson's biomarkers have been made. They have found abnormal alpha-synuclein as an indicator in most people with Parkinson's disease. A tool by the name of α-synuclein

seeding amplification assay created the confirmation, showing the marker in 93% of Parkinson's patients (Siderowf, MD & Concha-Marambio, Ph.D. et. al, 2023). Alpha-synuclein alterations within its aggregation properties are reasoning for Parkinson's occurrence. In animal models, Parkinson's has shown mitochondrial mishap which ends in neurotoxicity (Winklhofer, Haass, 2010). This is an important breakthrough that can be used to investigate therapies to target alpha-synuclein and reach Parkinson's at an early stage.

Currently, many trials of anti-alpha-synuclein antibody medication are in the process. Two notable ones that have occurred are the PASADENA and the SPARK studies. The antibodies: Prazinezumab and Cinpanemab, are aimed to work to neutralize toxic versions of this protein to help neutralize and delay the progression of Parkinson's disease, making sure the spread of the protein is limited (Kallunki, Ph.D., 2016). The hope is to help Parkinson's patients through monoclonal antibody immunotherapies, which the possibilities of will be discussed in the following pages. These trials have had ups and downs which have contributed to advancements in knowledge of Parkinson's and great possibilities for these therapeutics.

Introduction

Monoclonal Antibody Immunotherapy

Monoclonal antibodies work by specifically targeting only one antigen since they are lab-built. They are cloning only one specific antibody, unlike polyclonal antibodies which are binding to more than one type of antigen. They work to kill unwanted cells in a safer, more produced way.

One example of the success of these kinds of therapies in neurodegenerative diseases has been seen in Alzheimer's Disease. Alzheimer's disease is a form of dementia affecting cognitive and behavioral functions. This type of dementia usually affects older populations and is most common. It is a neurodegenerative disease that disconnects neural networks within the brain and its surrounding areas. It plays a factor in neural destruction and the decline of memory centers.

Currently, in the United States, there are two approved anti-amyloid monoclonal antibodies for Alzheimer's disease the Food and Drug Administration. The first one is Lecanemab, also known by its brand name of Leqembi®. Secondly, is the antibody by the name of aducanumab, also known by its brand name of Aduhelm®. There are also currently many of them in trial, not currently approved by the FDA, one being Donanemab.

These therapeutic antibodies which are fighting against Alzheimers are pinned as a phenomenon called anti-amyloid. Anti-amyloid (which has also shown signs of alpha-synuclein, making it a synucleinopathy) antibodies refer to antibody therapies that target the progression of Alzheimer's disease. It works to slow the decline of the patient during the span of Alzheimer's. Overall, these work by the removal of beta-amyloid, a plaque-forming protein targeting the brain. This causes the changes in the brain to slow down, allowing better life in patients. These drugs are transferred into the body through infusion therapy which is given every few weeks or monthly depending on the specific antibody.

Parkinson's disease, like Alzheimer's, has a variety of antibodies targeting the creator of the disease. In this case, it is alpha-synuclein proteins causing the appearance of the Lewy Bodies. Alpha-synuclein has many found antibodies that can be used to target Parkinson's in the future and be used to create more immunotherapies.

Type of Antibody	Name	The area of Alpha-Synuclein being targeted	Substantial effect on Alpha-Synuclein during

			the trial?
Passive	Prasinezumab	C-Terminus	No
	Cinpanemab	N-Terminus	No
Active	PD01A (AFFITOPE)	C-Terminus	Yes
	UB-312 (Vaxxinity)	C-Terminus	Yes

Figure 3. An overview includes information on various antibody therapies trialed or previously trialed against aggregated alpha-synuclein (Jain, 2024).

Methods

I came up with the study after initially researching antibody therapies in Alzheimer's Disease, then I wondered if there were similar treatments for PD. For my research, I used clinicaltrials.gov and science libraries/journals to find ongoing and finished trials and collect data to support my question. This was all done to collect data from previous trials and see what is currently working in therapies and what therapies are in the process. With that, analyzing what went wrong for future audiences to understand. I was able to collect various data sets of each type of antibody from a variety of scholarly sources to compile to allow for a consensus to ensue in the results. Doing a literary review, I was able to find a general answer to my investigation question on the antibody treatments for alpha-synuclein.

Related Literature

Passive

Passive immunotherapy is one subcategory of immunotherapies used in the medical world. Passive immunotherapy is where an (monoclonal) antibody or immune-cell factor is injected or given directly to a patient, instead of them getting something to create that in their body. Passive immunotherapy allows for a process of immediate action, but a downfall is that it isn't a long-term solution that the body keeps a memory of. Passive allows for quick results, but not long-term memory of the body's immune system to repeatedly fight the antigen when it appears in the body. Current research on active therapies for PD includes the study using Prasinezumab in the PASADENA trial. Another antibody is Cinpanemab in the SPARK trial. Prasinezumab specifically works by recognizing the C-terminal of α-synuclein and binds well to aggregated and monomeric proteins. While Cinpanemab recognizes the N-terminal and has a low binding affinity to monomeric α-synuclein (Pagano, et al. 2022).

Prasinezumab (PASADENA) Trial

A study published in the New England Journal of Medicine showed the possibility of Prasinenuzmab in the fight against Parkinson's Disease. Prasinenezumab works by targeting aggregated a-synuclein, a protein that is a factor of cause in Parkinson's Disease. With its last trial being phase 2, 316 patients who were victims of early-stage Parkinson's Disease were given a placebo or two levels of doses of the antibody. The participants were split up into 3 different groups: 105 participants receiving placebo, 105 participants receiving 1500mg of Prasinezumab, and 106 participants receiving 4500mg of Prasinezumab. The end goal was to change the rating

of the participants on the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) within the 52 weeks of the study. This scale works by measuring the impairment of Parkinson's from a scale of 0 to 236, which was hypothesized to reduce through the PASADENA trial. Another indicator used to see the efficacy of the antibody, Prasinezumab, was to measure the dopamine transporter levels in the putamen to the area of the body that was affected by Parkinson's Disease. The trial ended up not giving the results that were hoped. The MDS-UPDRS scores were similar across the board of doses, even the placebo. The dopamine transfer levels were also similar between all trial groups. Though no reasonable effects were found on the target, the trial gave information for further phases and trials of passive solutions to defeat aggregated alpha-synuclein.

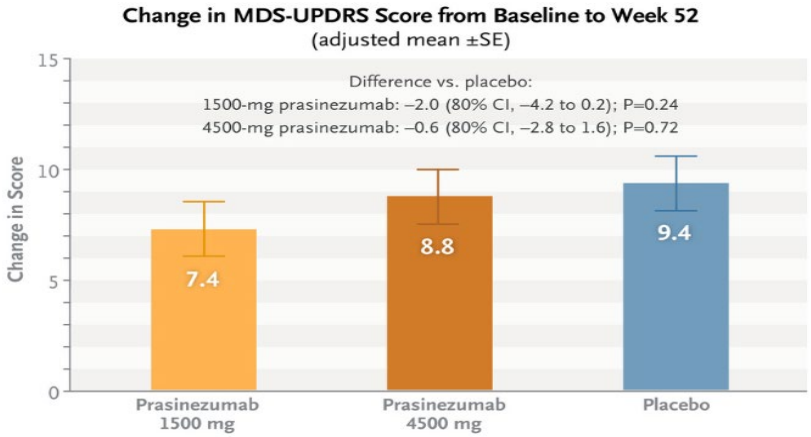

Figure 4. Graphed results of MDS-UPDRS scores after the 52-week trial period of Prasinezumab (Pagano, MD, et. al, 2022).

Cinpanemab (SPARK) Trial

A separate study published in the New England Journal of Medicine used the antibody Cinpanemab to treat aggregated alpha-synuclein in Parkinson's Disease. In a double-blind study with one placebo group and three groups of Cinpanemab of different doses, 357 participants were trialed. There was one placebo group, Cinpanemab at 250mg, 1250mg, and 3500mg every 4 weeks. In this trial, the same rating scale of MDS-UPDRS was used from 0 to 236 and it also secondarily observed dopamine transport levels using single-photon-emission computed tomography. Similar to Prazinezumab, the difference between the trial groups and the placebo wasn't that apparent and the dopamine transmission showed no difference. The trial was even taken to 72 weeks and then paused due to lack of efficacy.

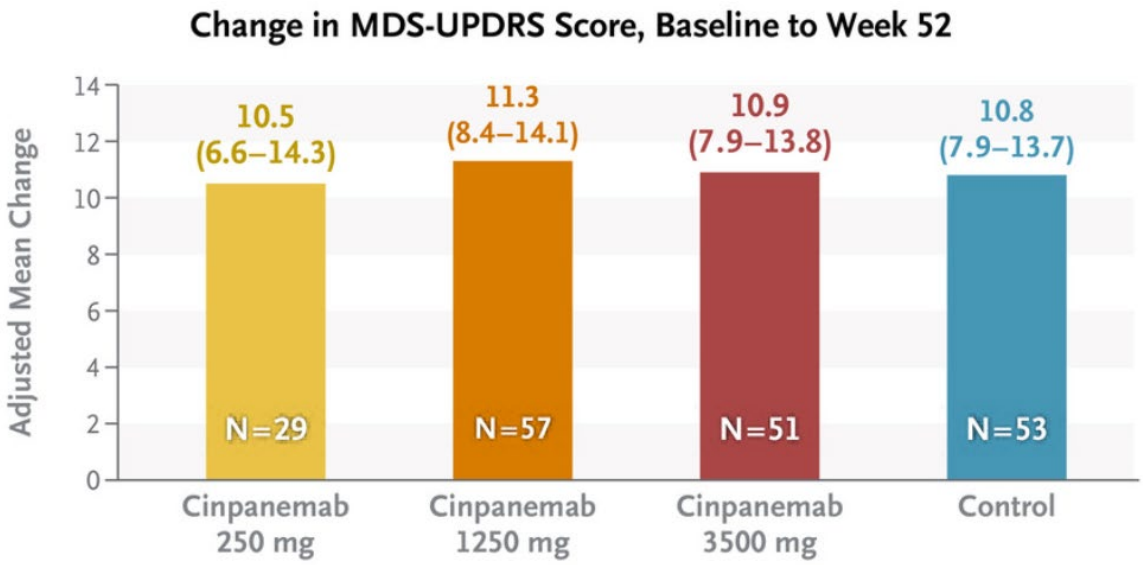

Figure 5. Graphed results of MDS-UPDRS scores after the 52-week trial period of Cinpanemab (Lang, MD, et. al, 2022).

Active

In contrast to passive immunotherapy, active immunotherapy creates immune system memory in the body. It is administered through paternal or third-party mononuclear cell immunization (Kutteh MD, PhD, HCLD, Stephenson MD, MSc, 2006). It is where a vaccination is given, one that prompts an immune response like antibodies created within the body, to attack an antigen long term. This method promotes immune system memory, unlike passive immunotherapy which is just one-and-done.

PD01A (AFFITOPE)

One of the most known active vaccinations for alpha-synuclein is AFFITOPE clinically known as PD01A. This immunization started with the testing on animal mice models and was successful "Immunization of two mouse lines overexpressing human α-synuclein lowered brain levels of aggregated α-synuclein, reduced neurodegeneration, and improved memory and motor behaviors" (Mandler, et. al 2014). The immunogen being presented is one of an eight-amino acid peptide sequence. This is made to act as an epitope in the C-terminal region of the human oligomeric alpha-synuclein, but it has a different sequence of amino acids (Alzforum, nd). It creates a limit to the spread of aggregated protein which is causing Parkinson's in the animal models it has been tested on.

The phase 1 trial for PD01A started in February of 2012 by the company AFFiRis and investigated populations ages 45-65 with Parkinson's Disease. Patients were randomly selected to receive the different doses of the PD01A immunization. First, they were selected to either receive 15 µg or 75 µg PD01A, which was then injected into the patient's upper arms. Then patients were followed up at 52 weeks and 39 weeks to see effects. After that, a first booster was given randomly at 15 µg or 75 µg and then the patients were followed up for 24 weeks. Finally, they all were given a second booster of 75 µg and then followed up for 52 weeks. The trial found that antibodies grew for the peptide, then fell after two years, but was said to be easily reactivated with any booster doses if needed. It was found that PD01A was safe to use on patients and that an immune response was detected and reported, though phase 2 will be needed for further investigations for its use in Parkinson's (Volc et. al, 2020).

UB-312 Vaxxinity

UB-312 is a vaccine created to build immunity upon alpha-synuclein by the company Vaxxinity. A peptide ends up attaching to the C-terminus of the alpha-synuclein which in turn activates T-cells which help the body fight the disease within it. First, UB-312 was tested in guinea pig and mice models where it was found that within the mice models there were reduced alpha-synuclein oligomers within the mice and an increase in motor skills when tested. The first phase started with injecting 50 healthy people who were given injections of 40 to 2,000 µg UB-312 or placebo at weeks 1, 5, and 13, in eight different dose groups (Yu et al., 2022). It was found that within the blood of these participants, the antibody had reached therapeutic levels. To test the vaccine in patients with Parkinson's, 20 participants were enrolled in the study who will get three doses of either 100 or 300 µg UB-312 or placebo on the 13-week schedule (Alzforum, 2023). In mid-2023, the results of this study were released, informing that 92% of participants had successfully developed antibodies against alpha-synuclein (Ciccone, 2023).

Relevance in Parkinson's Disease

Parkinson's is a fairly prevalent neurodegenerative disorder where a cure isn't yet certain. Previously, in other neurodegenerative diseases similar to Parkinson's many advancements have been made in terms of antibody treatments. Parkinson's affects motor skills in a patient, causing even the slowing of the disease's pathogenesis to better the day-to-day life of an individual with the disease. Targeting the center of the disease allows for a hope to have a long-term solution to this dire issue. Active treatments will allow for the body of patients to build long-term immunity and eventual success in passive treatments will allow for a quicker and less invasive solution to the issue.

Results and Discussion

Overall, the results showed that active therapies were more successful than passive ones. PD01A and UB-312 are viable vaccination options for those with Parkinson's, though the consensus shows that any therapy given won't remove Parkinson's, only make the pathogenesis slower and possibly reduce symptoms. The passive therapies are still working on further phases, working towards gathering more information as treatment worked on mice models.

Conclusion

It was found that active therapies are more effective in showing a difference in progression and symptoms while passive therapies are not showing the desired effects. The two passive antibodies investigated were Prazinezumab and Cinpanemab which were trialed and found to have no substantial differences from their placebos at the end of the study. The active, antibody-inducing therapies were PD01A and UB-312 which showed a more hopeful success due to the body's nature to make its memory. The goal is now to find the difference between humans and mice to see where the treatment differs, which I recommend discovering in future studies of this topic. Since we are seeing success in animal models and not humans, there must be a discrepancy between the biological and genetic factors within the two species, which when pinpointed can help convey results. Also, working to try these treatments on people at different stages of Parkinson's may allow for some more results. A lot of the studies were done on early-stage Parkinson's patients, who may have a different response than those who have had it for a while. The effect may be there, but not being seen significantly due to the limitation of disease stage and type. My research works to contribute by creating a place of information for current trials

and therapies for Parkinson's and what went wrong and right with them. It can help further innovation in the field of Parkinson's therapeutics and teach future studies what is currently available in society for people with this physically debilitating condition. One day, the hope is to have an FDA-approved treatment for folks with Parkinson's (or other synucleinopathies) in the least invasive way possible through alpha-synuclein antibodies.

Limitations and Error Analysis

My research was done through a review of other credible sources, rather than conducting my own study. One thing that could have enhanced the specificity of my investigation was looking at the same antibody type (for example Pranizeumab) in both active and passive, to see how they differ in that manner and rule out the possibility for the difference to be in the antibody itself. However, my research suggests that this is not true. A more detailed exploration could have been done on either one of the antibody types, but the purpose of the paper was to concisely describe what was being trialed on the market and its outcomes.

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Dr. Jobin Varkey, Ph.D. helped me so much with getting the science correct behind my studies. He worked to give us adequate background knowledge and helped us learn how to read papers and find sources. Professor Virgel helped a lot with the formatting of our paper and the ethics behind it. He made sure to teach us to accurately give credit to our sources and how to encapsulate everything in our paper. Also, a big thank you to the Gifted Gabber team and Coach Jo for allowing me this opportunity. The neuroscience research helped me a lot with figuring out the research process and how to formulate a review research paper. I found the aspect of finding opportunities for innovation the most thrilling.

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