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Commentary

Prasinezumab and Cinpanemab – The Perspective of a Person with Parkinson's

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Parkinson's disease follows an inexorable path of decline with worsening of symptoms and appearance of new ones, albeit in a heterogenous way with variation from person to person and variation from day to day. People with Parkinson's (PwP) have a great need for agents that will slow or stop this progression, but despite the large investment of money and time, no proven "disease-modifying" therapies are in clinical use. Recent hopes had been high for trials conducted by two of the largest pharmaceutical companies in the world, Biogen and Roche, and the full results of these studies are now published in the *New England Journal of Medicine* [1, 2].

The full spectrum of such projects is reflected in the Parkinson's Hope List [3], a database of therapies in development for Parkinson's. It represents my hope that something will emerge from the approximately 370 active projects that will impact my Parkinson's to enable normal living for my remaining years.

Many projects in the Hope List target the protein α-synuclein, widely thought to be a key part of the pathology of Parkinson's. The hypothesis is that aggregation of monomeric α-synuclein into oligomers and fibrils not only kills the neuron, but also spreads the pathology in a prion-like manner. If the spread of extracellular α-synuclein can be stopped, for example, by an antibody with selective high affinity for the aggregated forms, the subsequent clinical decline can be stopped in its tracks. As yet, there is no clinical validation for this theory and indeed there is an alternative school of thought that believes the active reduction of α-synuclein is potentially harmful to patients, by removing α-synuclein from its normal role in the cell. This has led to substantial debate in the Parkinson's scientific community on the role of α-synuclein and drugs that target its aggregation.

Consequently, there was a lot riding on the results of the two phase 2 clinical trials involving prasinezumab from Roche and cinpanemab from Biogen. The top line results were known already, with neither therapy showing any difference to placebo on primary outcome measures. The Roche results were originally presented in a conference poster [4], and Biogen's brief announcement was made in early 2021. Unfortunately, prasinezumab and cinpanemab join an unfortunate list of immunotherapies for neurodegenerative diseases that have not met their primary outcomes in clinical trials [5]. Thus, the question remains as to whether protein aggregation and spread are primary factors in these diseases.

Frankly, I don't think that PwP really care much about the mechanism of action. We care primarily for what will keep us feeling better for longer. Neither cinpanemab nor prasinezumab will be on a pharmacy shelf any time soon so, from the patient perspective, the trials failed.

I think PwP know and accept that trials will fail. If there is no failure, there is no ambition or risk being taken. The Hope List is just like many other

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project portfolios, with some destined for oblivion and probably a small number that will succeed. If only we knew which ones.

The Roche and Biogen studies were great hopes, with a lot of financial investment from large, highly competent companies. The investment was not only in money. As participants in clinical trials, PwP have a strong vested interest in a successful outcome – we have hope and invest it in the trials in which we participate.

So, what can we learn? First, that the participants will feel the blow of failure at least as much as anybody else involved. Almost 700 PwP invested their time, clinical samples and hope in the trials for cinpanemab and prasinezumab. PwP benefit in many ways through participation in clinical trials and, of course, want their efforts to result in success. This participation also involves an element of personal risk which we hope is worthwhile. Trial failure erodes hope and creates doubt in future participation, but is an inevitable consequence of the clinical trials process.

Second, failure should involve active learning. Despite the lack of success in therapies based on the aggregation and spread hypotheses in neurodegenerative disease, work continues. While Biogen's development has been stopped, Roche is continuing with a new phase 2b study, PADOVA, with more participants and different outcome measures. Abbvie have abandoned their anti-α-synuclein antibody projects "for strategic reasons". Meanwhile, at lease three anti-α-synuclein antibodies are in clinical development, from Astra Zeneca, Lundbeck and UCB, all of them currently in phase 1. Vaxxinity and AC Immune are trying an active immunisation approach with the same objective, and the latter project is at the start of phase 2. A further ten antibody projects are in discovery and pre-clinical [3]. We must stop and think of the demands placed on patients to participate in such trials. Hope and confidence are linked, and investor confidence in this class of therapies is also likely to diminish.

Third, in an ideal world without any constraints, we would run linear development programs where an activity would only start once the previous step had been successfully completed. So, for example, clinical studies that target α-synuclein removal would not happen until the fundamental mechanisms and the relationship to clinical symptoms were understood. We would also understand how to stratify patients into sub-types that would receive the most appropriate drugs, and have objective, accurate and relevant outcome measures. For existing PwP, it will take too long to reach these milestones. We have lives that need to be improved now. Today. Tomorrow is too late. I do not know the solution, but I do know that solving all these problems is the challenge to the world of Parkinson's science.

And last but certainly not least, we should pay tribute to the PwP who took part in these trials. With almost 900 active clinical trials for Parkinson's registered on clinicaltrials.gov, both interventional and observational, many more of us will be needed in the coming years.

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