Journal of Parkinson's Disease 12 (2022) 2293–2296
DOI 10.3233/JPD-229008
IOS Press

Commentary

This is NOT the End for Immunotherapy in Parkinson's Disease – A Perspective from Early Drug Development Scientists

Patrik Brundin[a,*], Hanno Svoboda[a,b], Azad Bonni[a] and Gennaro Pagano[a]
[a]*Neuroscience and Rare Diseases, Roche Pharma Research and Early Development, Roche Innovation Center Basel, Roche Ltd, Basel, Switzerland*
[b]*Roche Diagnostics GmbH, Penzberg, Germany*

Pre-press 15 November 2022

The results from two Phase II clinical trials testing the safety and efficacy of passive immunotherapy against aggregated alpha-synuclein in individuals with early-stage Parkinson's disease (PD) were reported in a recent issue of the New England Journal of Medicine. Prasinezumab (Roche/Prothena) [1] and Cinpanemab (Biogen) [2] showed good safety and tolerability, with mild infusion reactions in the treated groups and no immunogenicity concerns. However, in both studies, the primary endpoint (change from baseline in the Movement Disorders Society revised Unified Parkinson's Disease Rating scale, MDS-UPDRS, sum of Parts I + II+III) was not met. In a commentary accompanying these immunotherapy trials, Dr Alan Whone asks if this is "The End" for immunotherapies targeting alpha-synuclein in PD, and states "it does seem likely that the evidence in aggregate marks the end of the road for monoclonal antibodies in the treatment of early PD" [3]. In this brief commentary, we discuss possible reasons why PASADENA, the prasinezumab trial, did not meet its primary endpoint. We also describe what we learned from the outcomes of PASADENA, and why we think this is just the beginning (and not the end) of immunotherapy in PD. Finally, we state why we have decided to continue exploring prasinezumab in a new Phase IIb study in PD, namely the PADOVA trial, and briefly discuss what the new trial might teach us.

The development of immunotherapies targeting alpha-synuclein aggregation was encouraged during the past decade by a wealth of genetic, neuropathological and experimental model evidence suggesting that alpha-synuclein aggregates play an important role in PD pathogenesis (for reviews see refs [4, 5]). Several clinical development programs using immunotherapy were launched with significantly different approaches. These differences include, among others, the focus on passive versus active immunization and the antibodies targeting different alpha-synuclein epitopes (and possibly different forms of alpha-synuclein assemblies). The active immunotherapy approach developed by AFFITOPE (AC Immune), a vaccine derived by using short peptides [6], and prasinezumab are directed against the C-terminus of alpha-synuclein and bind with high affinity and avidity to aggregated alpha-synuclein, as well as the monomeric protein and other species [7]. Cinpanemab is directed against the N-terminal of

*Correspondence to: Patrik Brundin, Roche Pharma Research and Early Development, Roche Innovation Center Basel, Grenzacherstr. 124, 4070 Basel, Switzerland E-mail: Patrik.brundin@roche.com.

ISSN 1877-7171/$35.00

alpha-synuclein and has been shown to bind almost exclusively aggregated alpha-synuclein [2, 7].

In the PASADENA study, 316 individuals with early-stage PD were randomized 1:1:1 to receive monthly intravenous infusions of two different doses of prasinezumab or placebo. While PASADENA did not meet its primary endpoint at week 52 following the start of the treatment (Part 1 of the study), prasinezumab showed a favorable safety profile. Furthermore, at week 52, participants who were treated with prasinezumab exhibited a reduced decline of motor function (changes from baseline both in the MDS-UPDRS Part III score and in motor assessments using digital devices).

Several potential explanations exist for why the PASADENA study did not meet its primary endpoint. *First*, it is possible that the form(s) of aggregated alpha-synuclein targeted by prasinezumab are not the key drivers of disease progression in early-stage PD. That would imply that this form(s) of aggregated alpha-synuclein is not a valid therapeutic target for PD and that reducing its size or number at this stage of the disease might not be beneficial to slow/halt disease progression (see [8] for further discussion).

Second, it is possible that prasinezumab did not sufficiently remove aggregated alpha-synuclein in the brain. The doses of prasinezumab used in PASADENA showed good peripheral target engagement in the blood [9], but was not possible to measure central target engagement because biomarkers for brain aggregated alpha-synuclein are currently not available. Thus, we cannot conclude that the doses used in the trial were able to fully saturate the target. This highlights the importance of current efforts to develop a central biomarker of alpha-synuclein, either by brain imaging or using cerebrospinal fluid.

Third, we cannot exclude that the composite score used as primary outcome was not sufficiently sensitive to measure a treatment effect in early-stage PD. The MDS-UPDRS sum of Parts *I* + II+III (self-reported non-motor [Part I] and motor [Part II] Activities of Daily Living (ADL) and a clinician examination of motor signs [Part III]) was used as primary outcome because it is considered a global measure of PD severity. Notably, the MDS-UPDRS Parts I and II components change very little over 52 weeks in early-stage PD [10] and therefore are not ideal measures when exploring possible short-term changes in early disease trajectory induced by a non-symptomatic therapeutic intervention. To demonstrate the beneficial effect of an intervention designed to slow the course of a disease, there must be adequate disease progression to measure. In individuals with early PD, progression in a 52-week timeframe is most evident on MDS-UPDRS Part III relative to other components of the MDS-UPDRS scale (e.g., Parts I and II), and in other measures assessing motor symptoms. Indeed, when we compared the decline in motor function assessed by MDS-UPDRS Part III or with the digital motor score as exploratory outcomes, the placebo-treated group showed more rapid deterioration than both the prasinezumab-treated groups. However, formal statistical testing was not appropriate, since the primary endpoint was not met. Nonetheless, this suggests that prasinezumab might influence the rate of signs progression of motor signs in early PD. Therefore, focusing on a primary outcome measure in the motor domain that shows greater changes early in disease might have been more appropriate in this population.

Fourth, a longer duration of treatment might be necessary to detect significant benefits. Specifically, a lack of efficacy in the primary endpoint might have been due to the 52-week treatment duration being too short to capture a difference between active and placebo arms in PD which progresses slowly over decades, from prodromal to advanced clinical stages. Therefore, it is particularly important to note that all participants were provided with the opportunity to continue in Part 2 (52 weeks on prasinezumab) in which potential longer term efficacy on disease progression was evaluated. Thus, Part 2 of the PASADENA study was designed so that after Part 1 all the participants were given prasinezumab and were followed up to week 104. Notably, the outcome of Part 2 indicated that participants treated with prasinezumab for 104 weeks (early-start group) showed less decline in motor signs progression than participants treated with prasinezumab for 52 weeks only (delayed-start group), as indicated by MDS-UPDRS Part III scores at week 104. We also hope to learn more from an ongoing 5-year Open Label Extension which some of the participants have elected to join (PASADENA Part 3, to be completed in 2024). Part 3 will provide of prasinezumab long-term safety and efficacy data, by comparing with a real-world data arm derived from observational and placebo arms of clinical trials in early PD.

Fifth, it is known that people with PD exhibit varying rates of symptom progression. In PASADENA, we did not stratify participants recruited into the trial which meant that we included both those with

rapid progression and those who would be predicted to have a slower course. This means that the inter-individual variation in rates of decline within all groups was high and it also means that we included participants showing little functional decline. We also performed a pre-specified analysis evaluating faster-progressing subgroups in the PASADENA trial. One of the subgroups of faster-progressing individuals among early-stage PD was defined by including people who required a prescription of a MAO-B inhibitor, which we postulated to be on a faster progression trajectory compared with individuals who do not require this mild symptomatic treatment. When we examined the motor progression with MDS-UPDRS part III and digital biomarker results, the pre-specified subgroups with faster worsening of motor function revealed greater differences between the prasinezumab and placebo groups. These results should be interpreted with caution given the small sample sizes. That said, future trials could consider enriching for participants with faster progression, both to reduce variability within the groups and increase the power of detecting a true treatment effect.

Based on PASADENA results, we decided to continue exploring the therapeutic potential of prasinezumab. Our decision to continue was based on the results of secondary and exploratory outcomes. The new Phase 2b trial, named PADOVA, was initiated to evaluate the efficacy and safety of prasinezumab versus placebo in participants with early-stage PD who are on stable symptomatic PD medication such as people who required a prescription of a MAO-B inhibitor, which might represent a faster-progressing subgroup of early-stage PD. The MDS-UPDRS Part III was selected as primary outcome, measured as time to first meaningful progression of motor signs (increase of ≥ 5 points on MDS-UPDRS Part III from baseline).

PASADENA has taught us several lessons about how we should design trials aimed at measuring slowing of disease progression in PD. It might seem self evident, but a drug designed to slow the progression of PD will only show an effect in participants that progress over the course of the trial, and only in the specific measures that assess this decline. In that regard, MDS-UPDRS, sum of Parts *I* + II+III is not an ideal measure of progression in early-stage PD. Furthermore, the progression of symptoms in PD is not only slow, but also heterogeneous between patients, and the relative importance of a given pathogenetic mechanism might vary over the course of the disease. Therefore, it is of paramount importance to select the most appropriate patient population where the proposed mechanism of action of the new drug is likely to be most pertinent. In addition, it is vital to optimize outcome measures so they assess changes that are relevant to the patients daily functions and follow these changes over a sufficiently long span of time. Considering all the challenges that complex neurodegenerative diseases present, failures are almost inevitable during the early development of new therapies. We are extremely grateful to the trial participants and their families for their vital contributions to these trials, and also value immensely their input on the journey towards what we hope will be a new and effective therapy for PD. It is essential to learn from every trial, and rather than viewing PASADENA as the end of the development of immunotherapies in PD, we think it might represent the end of the beginning of the quest for a disease-modifying therapy in PD.

CONFLICTS OF INTEREST

All the authors are employees and hold shares in F. Hoffmann-La Roche. Gennaro Pagano is a shareholder of Atea Pharmaceuticals, Novartis and Eli Lilly and Companies Limited and Patrik Brundin is a shareholder of Acousort AB, Axial Therapeutics, Enterin Inc and RYNE Biotechnology.

REFERENCES

[1] Pagano G, et al. (2022) Trial of Prasinezumab in Early-Stage Parkinson's Disease. *New Engl J Med* **387**, 421-432.
[2] Lang AE, et al. (2022) Trial of Cinpanemab in Early Parkinson's Disease. *New Engl J Med* **387**, 408-420.
[3] Whone A (2022) Monoclonal Antibody Therapy in Parkinson's Disease — The End? *New Engl J Med* **387**, 466-467.
[4] Brundin P, Dave KD, Kordower JH (2017) Therapeutic approaches to target alpha-synuclein pathology. *Exp Neurol* **298**, 225-235.
[5] Jasutkar HG, Oh SE, Mouradian MM (2022) Therapeutics in the Pipeline Targeting α-Synuclein for Parkinson's Disease. *Pharmacol Rev* **74**, 207-237.
[6] Volc D, et al. (2020) Safety and immunogenicity of the α-synuclein active immunotherapeutic PD01A in patients with Parkinson's disease: a randomised, single-blinded, phase 1 trial. Lancet Neurology **19**, 591-600.
[7] Games D, et al. (2014) Reducing C-Terminal-Truncated Alpha-Synuclein by Immunotherapy Attenuates Neurodegeneration and Propagation in Parkinson's Disease-Like Models. *J Neurosci* **34**, 9441-9454.
[8] Espay AJ, et al. (2019) Revisiting protein aggregation as pathogenic in sporadic Parkinson and Alzheimer diseases. *Neurology* **92**, 329-337.

[9] Jankovic J, et al. (2018) Safety and Tolerability of Multiple Ascending Doses of PRX002/RG7935, an Anti–α-Synuclein Monoclonal Antibody, in Patients With Parkinson Disease. *Jama Neurol* **1**, 9. doi:10.1001/jamaneurol.2018.1487

[10] Jackson H, et al. (2021) Hoehn and Yahr Stage and Striatal Dat-SPECT Uptake are Predictors of Parkinson's Disease Motor Progression. *Front Neurosci* **15**, 765765. doi: 10.3389/fnins.2021.765765.