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Editorial

Monoclonal Antibodies in Neurodegenerative Disease May Work, But They Don't Help: A Perspective from Physicians

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Removing misfolded protein depositions from the brain, or preventing them from accumulating altogether, seems like a rational therapeutic approach to arrest the process of neurodegeneration in persons with diseases in which these depositions are a key pathology. Alpha-synuclein would be the quintessential protein to target in Parkinson's disease (PD). Since considerable and irreversible neurodegeneration has already occurred at the time of the clinical diagnosis, early treatment should be the aim.

Two recent phase II clinical trials in PD patients tested this hypothesis, by treating levodopa-naïve patients with early-stage PD with monoclonal antibodies—in the SPARK study, intravenously administered cinpanemab [1] and in the PASADENA study, intravenous prasinezumab [2]. Unfortunately, both trials failed to show clinical effectiveness of these monoclonal antibodies against alpha-synuclein. These findings are reminiscent of earlier neutral studies in the Alzheimer's disease (AD) field [3]. Taken together, these findings are grounds to reconsider the generic approach of monoclonal antibodies against specific proteins in neurodegenerative diseases.

In the AD trials, anti-amyloid-beta therapy does actually remove amyloid-beta from the brain, but the treatment does not improve cognition [4]. Similarly, targeting tau also affects tau levels in cerebrospinal fluid, but again without effect on clinical outcomes [5]. In the two recent PD trials, the dopamine transporter as assessed by DAT-SPECT scan was used to measure the biological outcome. In both trials, there was no change in SPECT signal. Whether the antibody therapy affected alpha-synuclein levels in the brain was thus not established in the two studies. This raises two questions: first, whether the anti-alpha-synuclein therapies actually had any biological effect, i.e., whether they were able to remove alpha-synuclein from the brain at all; and second, whether it is reasonable to assume that, even if alpha-synuclein

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was removed successfully, this would be detectable as a change in signal on a DAT-SPECT scan, i.e., whether this would be an appropriate surrogate outcome to demonstrate target engagement.

Several explanations have been suggested for the neutral findings in all these trials, including that the wrong population was targeted (e.g., those with too advanced disease) or that the outcomes were not sensitive enough. These arguments would imply that the trial designs were not appropriate, which we contend—these large trials were all designed very carefully and executed meticulously. Moreover, when we capitalize on the experience from the AD field, even in pre- or very early symptomatic genetic mutation carriers with considerable follow-up, no clinical effect could be established [6]. This experience in the AD field cautions against excessive hopes that anti-alpha-synuclein treatments will be dramatically more effective when delivered during the prodromal phase of PD. Another common explanation is that the wrong protein had been targeted, whether this being a monomer, oligomer, or aggregated form, or the wrong part of the alpha-synuclein protein. However, drawing from the lessons from the AD field, another reasonable explanation is that these drugs might actually work, i.e., they might successfully remove the targeted proteins, but that they do not help, as they do not improve symptoms or slow down clinical disease progression. Our understanding of these neurodegenerative diseases, and in particular the specific role of the different proteins involved, may be insufficient, and we should consider the unfortunate possibility that we may be chasing the wrong mechanism altogether. So, rather than seeking methodological explanations for the neutral trial results, we may have to accept that the null-hypothesis is true—namely that removing these proteins will not affect the clinical disease course.

New therapies targeting alpha-synuclein in different ways than with antibodies will appear. More sensitive outcome measures are being proposed, particularly using different biomarkers as proof of concept of target engagement, and the use of continuously recorded digital outcomes to objectively capture even subtle changes in disease status. But even when target engagement is shown, demonstration of tangible effects for patients remains essential. Meanwhile, alternative potentially disease-modifying approaches could be probed which are more agnostic to the specific underlying molecular mechanisms, including lifestyle interventions [7].

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CONFLICT OF INTEREST

Prof. Richard has no conflict of interest to report.

Prof. Bloem currently serves as co-Editor in Chief for the *Journal of Parkinson's Disease*, but was not involved in any way in the peer review process of this editorial. He serves on the editorial board of *Practical Neurology* and *Digital Biomarkers*, has received honoraria from serving on the scientific advisory board for Abbvie, Biogen, and UCB, has received fees for speaking at conferences from AbbVie, Zambon, Roche, GE Healthcare, and Bial, and has received research support from the Netherlands Organization for Scientific Research, the Michael J. Fox Foundation, UCB, Not Impossible, the Hersenstichting Nederland, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, and the Parkinson Vereniging (all paid to the institute).

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