Monoclonal Antibody Therapy in Parkinson’s Disease — The End?

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Parkinson’s disease is increasing in incidence at a faster rate than any other serious neurologic condition. Despite multiple agents putatively showing preclinical promise, there is no disease-modifying therapy available for clinical use in this disorder. Indeed, no potential treatment has survived scrutiny in a clinical trial to reach approval by a regulatory body.

Several target mechanisms have been identified by which to achieve neuroprotection or neurorestoration of dopaminergic neurons that are at the nexus of Parkinson’s disease. One approach, which engendered much hope, has been the targeting of the pathologically aggregated form of the protein α-synuclein. Studies of active immunotherapy directed at this target are in the early stage of clinical development, and there is laboratory evidence in support of a passive immunologic approach to reducing the concentration of abnormal α-synuclein through deployment of monoclonal antibodies. Two phase 2 trials of monoclonal antibodies for the treatment of Parkinson’s disease are reported in this issue of the Journal. These results have been keenly awaited, not least after the approval by the Food and Drug Administration of a monoclonal antibody, aducanumab, for the treatment of Alzheimer’s disease — a decision that, to say the least, has been controversial.

The investigations in Parkinson’s disease reported by Pagano et al. using prasinezumab (Phase 2 Trial of Anti α-Synuclein Antibody in Early Parkinson’s Disease [PASADENA]) and by Lang et al. using cinpanemab (SPARK trial) have very similar trial designs, making comparison of the results relatively straightforward. Both double-blind trials used the change in the sum of scores on parts I, II, and III of the Movement Disorder Society–Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) at 52 weeks as a primary end point. Each investigation then rolled over to a blinded phase, in which all the participants received active therapy. Similar numbers of participants were enrolled (316 in PASADENA and 357 in the SPARK trial), and the inclusion criteria specified an early stage of Parkinson’s disease for trial entry. Secondary end points included motor and nonmotor end points, such as MDS-UPDRS subscale scores, as well as neuroimaging to assess the rate of decline in dopamine terminal integrity with the use of dopamine transporter single-photon-emission computed tomography (DaT-SPECT). Both trials were conducted at multiple sites in North America and Europe, with the SPARK trial also recruiting in Israel, but the enrolled populations were not representative of a wider ethnic mix that exists for Parkinson’s disease in the United States and some other countries.

As for the results, neither trial showed benefit with respect to the primary or secondary end points save that there was a suggestion that treatment with low-dose prasinezumab slowed progression on a secondary end point, the score on MDS-UPDRS part III (clinician-conducted motor examination). However, the results for secondary end points were not adjusted for multiple comparisons, and hence no conclusions can be drawn from them. Moreover, both studies failed to show a difference between active treatment and placebo in DaT-SPECT imaging,
but it is generally acknowledged that this imaging method neither rules in nor rules out target engagement by monoclonal antibodies or altered α-synuclein clearance, because there is as yet no radioligand that permits such measurements. Neither of the extension phases of the trials, which afforded a delayed-start design, yielded positive results, with the follow-on period for the assessment of cinpanemab halted early owing to lack of efficacy. Nevertheless, should someone wish to try again from scratch — and it does remain possible that there is a temporal delay between clearance of aggregated α-synuclein and neuronal sparing and that a considerably longer trial duration may prove more successful — both agents seemed to be relatively safe and did not arouse immunogenicity concerns.

Although these results are more than disappointing and certainly have no implications for current practice, both teams should be congratulated. Completing and expertly delivering large-scale complex trials of intravenously administered monoclonal antibody therapies, which involved infusions every 4 weeks, and making composite outcome assessments that are appropriate for Parkinson's disease, all during a time that included the disruptions associated with the Covid-19 pandemic, is no small achievement. Furthermore, both PASADENA and the SPARK trial are models of participant retention, with 99% and 97%, respectively, of the participants remaining in the trial at the end of the primary stage. This, as well as other aspects of trial conduct, should provide guidance for future neuroprotective trials in Parkinson's disease.

The negative data have apparently not deterred the sponsor of PASADENA from commencing a phase 2b trial, although it does seem likely that the evidence in aggregate marks the end of the road for monoclonal antibodies in the treatment of early Parkinson's disease. Still, this should not dismiss the possibilities that success may yet be achieved with the same or similar agents in prodromal Parkinson's disease or in genetic forms of the disorder or that alternative mechanisms to affect aggregated α-synuclein may be beneficial. The results of the trials pose two broader questions: is the inability to show disease modification in Parkinson's disease due to preclinical research providing misleading encouragement? And, are current clinical trial designs delivering type II errors? For PASADENA and the SPARK trial, it seems that the former explanation is more likely, but the latter explanation remains possible; if true, that could imply that outcome measures should be more sophisticated and move into the digital age. Despite the pitiful lack of realization in disease-modifying therapy trials in Parkinson's disease, the field should not give up. A quotation from Winston Churchill perhaps needs bearing in mind: “Success consists of going from failure to failure without loss of enthusiasm.” After all, investigators and sponsors heading for the hills is unlikely to best serve people with Parkinson's disease.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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