Disputes & Debates: Editors' Choice

Editors' Note: Safety of AADC Gene Therapy for Moderately Advanced Parkinson Disease: Three-Year Outcomes From the PD-1101 Trial

In their phase 1b open-label clinical trial, the PD-1101 investigators reported the 36-month safety and efficacy findings after bilateral putaminal infusions of an adenoviral vaccine for patients with advanced Parkinson disease (PD). The vaccine encoded the human aromatic amino acid decarboxylase (AADC) gene, which is responsible for converting levodopa to dopamine, and whose presence declines with time in PD as striatal neurons degenerate. The trial reported no adverse safety events. Participants who received the highest dose of the adenoviral AADC vector required 21%–30% lower doses of PD medications, and there were generally stable or improved outcomes across motor and quality of life assessments. Kang et al. highlight how dopamine and its metabolites may be toxic to certain neurons because they lack the intracellular machinery necessary to sequester dopamine. Although local infusion of the AADC adenoviral vector appears promising over the short term, the long-term consequences of this procedure warrant further exploration. Furthermore, the risk-benefit of this procedure will need to be studied in clinical trials that examine various combinations of therapies that are now available to patients with advanced PD.

James E. Siegler, MD, and Steven Galetta, MD
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Reader Response: Safety of AADC Gene Therapy for Moderately Advanced Parkinson Disease: Three-Year Outcomes From the PD-1101 Trial

Un Jung Kang (New York), Ken Nakamura (San Francisco), and Xiaoxi Zhuang (Chicago)
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In a recent gene therapy trial, delivery of aromatic L-amino acid decarboxylase (AADC) to striatal cells reduced the levodopa dose required and improved global impression measures, with no apparent serious adverse effects.[1] This study builds on previous research that gene therapy to enhance dopamine production in specific target areas has the potential to enhance the motor benefits of levodopa.[2]

However, ectopic AADC introduced by adeno-associated virus gene therapy produces dopamine within the cytoplasm of transduced cells, mostly striatal neurons, before exiting the cells by unknown mechanisms to reach dopamine receptors on striatal target neurons. It is important that dopamine and its metabolites can be toxic to those nondopaminergic cells because they lack the ability to sequester dopamine in vesicles[3] and likely also lack the specialized antioxidant defenses that normally protect endogenous dopamine neurons.[4] Indeed, in a model study with mice, unregulated high levels of dopamine in striatal neurons, due to an overexpression of the dopamine transporter, produced profound dopamine-dependent oxidative neurodegeneration with necrotic morphology and striatal volume atrophy.[5] As such, it will be critical to consider the potential long-term toxicity of AADC gene therapy when combined with levodopa and whether

Author disclosures are available upon request (journal@neurology.org).

the risks are worthwhile, given that it remains unclear if the benefits significantly surpass those of current adjunct pharmacologic therapies.

1. Christine CW, Richardson RM, Van Laar AD, et al. Safety of AADC gene therapy for moderately advanced Parkinson disease: three-year outcomes from the PD-1101 trial. *Neurology*. 2022;98(1):e40-e50. doi:10.1212/WNL.0000000000012952.
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Author Response: Safety of AADC Gene Therapy for Moderately Advanced Parkinson Disease: Three-Year Outcomes From the PD-1101 Trial

Chadwick W. Christine (San Francisco), R. Mark Richardson (Cambridge, MA), Elisabeth M. Fine (Waltham, MA), Omar S. Khwaja (Basel, Switzerland), Grace S. Liang (San Diego), Andreas Meier (Cambridge, MA), Eiry W. Roberts (San Diego), Krystof Bankiewicz (San Francisco), and Paul S. Larson (Tucson)
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We appreciate the comment by Kang et al. on our research.[1] While we acknowledge findings of toxicity in a mouse model of elevated cellular dopamine due to overexpression of the dopamine transporter,[2] such toxicity has not been observed in rodent or primate models of Parkinson disease (PD) in which the aromatic L-amino acid decarboxylase (AADC) gene therapy was tested.[3,4] Moreover, in our observations of these participants 3 years after AADC therapy,[1] we did not see evidence of significant clinical worsening, which would be expected if the AADC gene therapy was causing injury to medium spiny neurons.

We agree that adjunctive treatments, such as dopamine agonists, monoamine oxidase-B inhibitors, or catechol-o-methyl transferase inhibitors, can ameliorate symptoms in moderately advanced PD. However, many of the participants in the 1,101 study were already taking these agents before participating in this study. We observed that participants on 1 or more of these adjunctive therapies obtained additional benefit after AADC gene therapy, although the small open label study design prevents definitive conclusions. Overall, it is our impression that AADC gene therapy was well tolerated at the concentrations used in this study.

1. Christine CW, Richardson RM, Van Laar AD, et al. Safety of AADC gene therapy for moderately advanced Parkinson disease: three-year outcomes from the PD-1101 trial. *Neurology*. 2022;98(1):e40-e50. doi:10.1212/WNL.0000000000012952.
2. Chen L, Ding Y, Cagniard B, et al. Unregulated cytosolic dopamine causes neurodegeneration associated with oxidative stress in mice. *J Neurosci*. 2008;28(2):425-433. doi:10.1523/JNEUROSCI.3602-07.2008.
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Reader Response: Safety of AADC Gene Therapy for Moderately Advanced Parkinson Disease: Three-Year Outcomes From the PD-1101 Trial

Jose-Alberto Palma (New York)
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I read with interest the report on the PD-1101 trial outcomes.[1] Adeno-associated virus (AAV) vectors used in gene therapy, including AAV2, can elicit humoral and T-cell responses against the viral capsid components in humans. These immune changes can affect the duration of transgene expression and also potentially affect the patient's safety.[2] Although the CNS has been traditionally considered an immune-privileged organ, preclinical studies with direct AAV delivery to the CNS have shown AAV-related markers of neuroinflammation and CNS pathology, including dorsal root ganglionopathy and white cell infiltration.[3-5] This indicates that direct AAV delivery to the CNS is not devoid of immunogenicity, which in many cases may be subclinical.

Christine et al. do not comment on these issues. Although they do mention that participants with preexisting anti-AAV2 antibodies were excluded, it is unknown whether anti-AAV2 antibodies in blood or CSF were measured at any time after AAV2 administration, or whether blood or CSF biomarkers of immune activation or inflammation were monitored. Although it is reassuring that no patient experienced an AAV-related serious adverse event, additional information on the immunogenicity aspects mentioned above would enhance the value of this report and its potential to inform future intraparenchymal gene therapy trials for CNS disorders.

1. Christine CW, Richardson RM, Van Laar AD, et al. Safety of AADC gene therapy for moderately advanced Parkinson disease: three-year outcomes from the PD-1101 trial. *Neurology*. 2022;98(1):e40-e50. doi:10.1212/WNL.0000000000012952.
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Chadwick W. Christine (San Francisco), R. Mark Richardson (Cambridge, MA), Amber Van Laar (Chapel Hill, NC), Elisabeth M. Fine (Waltham, MA), Omar S. Khwaja (Basel, Switzerland), Grace S. Liang (San Diego), Krystof Bankiewicz (San Francisco), and Paul S. Larson (Tucson)
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We appreciate the comment by Palma on our research.[1] The presence of serum AAV2 neutralizing antibodies (nAbs) was determined using a validated ELISA method at baseline and then at 1-, 3-, 6-, and 12-month postinfusion of AAV2-AADC gene therapy. At baseline, all treated participants met the inclusion criterion with nAb ≤1:1,200 and 11 participants (73%) had nAb below the lower limit of detection. Twelve months after administration of VY-AADC01, most participants (12, 80%) developed nAb at titers ranging from 1:57 to

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1:7,273, whereas 2 participants from cohort 1 and 1 participant from cohort 2 had no detectable nAb. Peak titers appeared at 6 months with either stable or lower titers at 12 months. Neither the presence of preexisting nAb above the detection limit nor an increase in nAb titer from baseline precluded an increase in 6-[^{18}F]fluoro-L-dopa uptake ratio after administration of VY-AADC01. These findings, along with the clinical stability of these participants over the 3-year study, suggest that an inflammatory response to AAV2 did not affect AADC gene expression.

1. Christine CW, Richardson RM, Van Laar AD, et al. Safety of AADC gene therapy for moderately advanced Parkinson disease: three-year outcomes from the PD-1101 trial. *Neurology*. 2022;98(1):e40-e50. doi:10.1212/WNL.0000000000012952.

CORRECTION

Distinguishing 3 Classes of Corpus Callosal Abnormalities in Consanguineous Families

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In the article "Distinguishing 3 Classes of Corpus Callosal Abnormalities in Consanguineous Families" by Hanna et al.,[1] the end of the Study Funding section should include the following: "H.K. was supported by a grant from TUBITAK (SBAG-108S418)." The authors regret the omission.

Reference

1. Hanna RM, Marsh SE, Swistun D, et al. Distinguishing 3 classes of corpus callosal abnormalities in consanguineous families. *Neurology*. 2011;76(4):373-382.

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