New Light Shed on Leucine-Rich Repeat Kinase 2 (LRRK2) Kinase Inhibitors in Parkinson's Disease

Daher JP, Abdelmotilib HA, Hu X, et al. Leucine-Rich Repeat Kinase 1 (LRRK2) Pharmacological Inhibition Abates α -Synuclein Gene-Induced Neurodegeneration. *J Biol Chem*. 2015;290:19433–19444.

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease. Neuroprotection remains elusive. Studies of monogenic PD may reveal new treatment approaches, but these are likely to be mutation or pathway-specific.

Leucine-rich repeat kinase 2 (*LRRK2*) causes 1% of sporadic PD and from 5% to 15% of autosomal dominant familial monogenic PD in Caucasians.¹ G2019S, the most common *LRRK2* mutation,¹ may cause kinase activity up-regulation, proinflammatory response enhancement, and neuron toxicity.²

Protein and lipid kinases are crucial in metabolism, cell signaling, and protein regulation.³ Pathological processes result from kinase deregulation, and the development of kinase inhibitors is important in neurotherapeutics.

Since 1995, there have been 30 approved kinase inhibitors and an additional 130 in development/trials.⁴ Kinase inhibitors are used in renal cancer (e.g., sorafenib), medullary thyroid cancer (vandetanib), nonsmall cell lung cancer (ceritinib, gefitinib), metastatic myeloma (verumafenib), chronic myeloid leukemia (imatinib, dasatinib), rheumatoid arthritis (tofacitinib), idiopathic pulmonary fibrosis (nintedanib), and in organ rejection therapy (everolimus). Known kinase inhibitors cover only 15% of the whole "kinome"; thus, there is potential for expansion.⁴ Kinase inhibitors may have a role in neurodegeneration abatement; however, toxicity limits their usefulness in humans.²

Daher et al.² investigated the effects of *LRRK2* kinase inhibition on α -synuclein neurodegeneration in a rat model. The right substantia nigra pars compacta (SNpc) of wild-type rats and transgenic G2019S rats was injected with adeno-associated viral vectors expressing α -synuclein. The rats also received an intrastriatal injection of a novel *LRRK2* kinase inhibitor (PF-06447475) or calcium carbonate (control) for 4 weeks.

PF-06447475 showed low-nanomolar *LRRK2* affinity, minimal inhibition of other kinases, and remarkable brain penetrance.⁵ The higher dose of 30 mg/kg for 14 days

maintained the half-maximal inhibitory concentration (IC₅₀). Both G2019S rats and wild-type rats showed almost complete ablation of Ser p335 *LRRK2* levels in brain, lung, and kidney with 30 mg/kg twice daily. Treatment was well tolerated, and there was no accumulation of CD68 myeloid cells or lysosomal associated membrane protein 1 (LAMP1)-positive organelles (found on the lymphocytes undergoing degranulation) in type 2 pneumocytes or in renal tubules. These were previously described in *LRRK2* knockout rats treated with other *LRRK2* kinase inhibitors.² Although *LRRK2* ablation was not complete in this study, the dosage achieved IC₉₀ inhibition for 18 hours daily, and activity levels were above the IC₅₀.

There was similar SNpc expression of human α -synuclein in G2019S rats and wild-type control rats 14 days post-viral transduction, with similar tyrosine hydroxylase (TH) staining and distribution compared with uninjected SNpc.² However, 4 weeks post-viral transduction nitrosylated/oxidized α -synuclein accumulation was found in the surviving TH-positive neurons in both groups.

There was a 20% loss of TH-positive neurons in wild-type rats compared with a 40% loss in G2019S rats with an associated decrease in ipsilateral dorsal striatal fiber density. Surgery alone did not increase the neurodegeneration.²

Of note PF-06447475 resulted in a nonsignificant TH-positive cell loss in both groups and led to the preservation of TH activity. PF-06447475 also abated G2019S neuroinflammation.²

Despite restricted *LRRK2* expression in rat brain, the authors surprisingly demonstrated that PF-06447475 attenuated α -synuclein-induced neurodegeneration in wild-type rats. They outlined the novel compound's potency, specificity, and bioavailability, which was superior to those of previous *LRRK2* kinase inhibitors.

This is an important research article that opens new avenues for the development of novel neuroprotective agents for PD. *LRRK2* kinase inhibitors may or may

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Relevant disclosures and conflicts of interest are listed at the end of this article.

Received 11 November 2015; revised 31 December 2015; accepted 9 January 2016.

Published online 11 February 2016 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12333

not need to be gene mutation-specific. Once the safety and appropriate time window for the use of PF-06447475 are determined, this approach holds promise for PD therapeutics.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

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T.L.: 3B

Disclosures

Funding Sources and Conflicts of Interest: The authors report no sources of funding.

Financial Disclosures for previous 12 months: The authors report no conflicts of interest. ■

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