Neuroscience 2015

Presentation Abstract

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Program#/Poster#:	12.01
Presentation Title:	Nilotinib significantly alters blood and CSF α-Synuclein and p-Tau levels, inhibits dopamine breakdown and increases neuro-restorative markers in an open-labelled Parkinson's disease with dementia and Lewy body dementia trial
Location:	N230
Presentation time:	Saturday, Oct 17, 2015, 1:00 PM - 1:15 PM
Topic:	++C.03.a. Human studies
Authors:	***F. L. PAGAN**; Georgetown Univ. Hosp. Neurol. Dept., Medstar Georgetown Univ. Hosp., Washington, DC
Abstract:	Parkinson's disease is characterized by loss of dopamine neurons and accumulation of α-Synuclein in LBs. Nilotinib is a potent inhibitor of Abl tyrosine kinase and it is FDA-approved for adult CML. Nilotinib penetrates the brain and inhibits Abl, leading to autophagic clearance of amyloid proteins. It also increased brain dopamine and modulated

immune markers, and reversed motor and cognitive decline. We conducted a clinical trial with the primary objective to determine the safety and efficacy of Nilotinib in advanced PD, PDD and LBD patients. Our studies include measurement of CSF and plasma biomarkers at baseline, 2 and 6 months with 150mg and 300mg Nilotinib daily. These doses are significantly lower of Nilotinib for CML treatment (800-1200mg/ day). We excluded patients with prolonged QTc and other medical contradictions. 8 patients have passed the 2 months period. More than half the patients screened were excluded due to cardiac complications. Nilotinib has a good safety profile in enrolled subjects with no QTc prolongation or myelosuppression. Nilotinib CSF penetration is 0.5-1.5%. A significant reduction (>60%) in plasma α-Synuclein was detected, correlating more frequent bowel movements. There is also a significant decrease in CSF p-Tau181, while total Tau is unchanged. CSF Abeta40 is reduced (18%) with no change in the plasma, while CSF and plasma Abeta42 remain stable. The level of CSF α-Synuclein is unchanged, suggesting stabilization of α-Synuclein levels. CSF homovanillic acid (HVA) is reduced (26%) at 2 months despite a decrease in dopamine replacement therapy, suggesting inhibition of dopamine breakdown. This effect on dopamine also correlates with clinical outcomes, including stabilization with less or no Azilect and L-Dopa. Nilotinib also increases CSF concentration (30-55%) of neuro-restorative markers (PDGF-AB/BB, G-CSF, IL-7, GRO, CCL2 and CCL5), while it reduces markers of neurodegeneration (NSE and S100B). Overall these data indicate safety, tolerability and biomarkers efficacy, and provide a collectively compelling rationale to examine Nilotinib in larger placebo-controlled, double blind studies in earlier stages of diseases.

Disclosures:	**F.L. Pagan:** A. Employment/Salary (full or part-time):; Georgetown University Hospital. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Lewy Body Foundation, Georgetown University Hospital. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Georgetown University Medical Center's CRU. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Teva, Acadia, US World Meds, Lunbeck, Abvie, Merz.
Keyword (s):	PARKINSON'S DISEASE
	ALPHA-SYNUCLEIN
	TAU
Support:	Lewi Body Disease Foundation

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