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Nilotinib In Parkinson's Disease: A Therapeutic Pathway Yet to Be Fulfilled

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ABSTRACT

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, characterised by the loss of dopaminergic neurons and accumulation of α-synuclein, resulting in the development of motor and non-motor symptoms. Multiple studies have demonstrated an increased activation of Abelson tyrosine kinase (c-Abl) in PD, suggesting that it is a potential target for treatment. Nilotinib, a selective c-Abl inhibitor approved to treat chronic myeloid leukemia, has demonstrated neuroprotective effects in preclinical PD models by reducing neurodegeneration and promoting α-synuclein clearance. This prompted further preliminary clinical studies, in which nilotinib was found to positively affect biomarker levels in cerebrospinal fluid (CSF) and enhance motor and cognitive outcomes in individuals with advanced PD. This review aims to analyze the efficacy of nilotinib as a potential disease-modifying treatment in PD.

Methods

In this study, we reviewed data from Randomized Control Trials (RCTs) and Meta-Analyses from PubMed, Scopus and Google Scholar, using keywords like "Parkinson's disease"and "nilotinib". Inclusion criteria included published papers in English from 2019 to 2024. Patients with comorbid conditions were excluded.

Results

Multiple clinical trials conducted over a 6 - 27 month period comparing nilotinib 150-mg and 300-mg to placebo-controlled groups, showed limited efficacy of the drug as a disease-modifying treatment for PD. Both nilotinib 150-mg and 300-mg caused an increase in CSF levels of dopamine metabolites - 3,4-

Dihydroxyphenylacetic Acid (DOPAC) and homovanillic acid (HVA) levels in the 150-mg group but no change in the 300-mg group. The levels of α-synuclein and total CSF α-synuclein were insignificant across all three groups. However, CSF oligomeric/total α-synuclein ratio was reduced in the nilotinib150-mg group as compared to the placebo group. Nilotinib at 150-mg was ineffective in improving motor symptoms or CSF biomarker levels due to insufficient central nervous system penetration. Additionally, the 300-mg groups showed improvements in the Unified Parkinson's Disease Rating Scale (UPDRS) when compared to the 150-mg groups. A higher incidence of serious adverse effects such as increased lipase levels, arthritis, and arrhythmias was notable in the 300-mg group, resulting in more premature withdrawals from the trials. Overall, the findings suggest that nilotinib is not a significant therapeutic option due to its overt adverse effects in patients with PD.

Conclusion

Although there is currently insufficient clinical evidence to support nilotinib as a successful disease-modifying treatment for PD, its assessment has provided important new information about the function of CNS-targeted therapies. Existing studies have shown that nilotinib can penetrate the blood brain barrier (BBB) and activate central dopaminergic pathways, as evidenced by slight changes in CSF biomarkers like DOPAC and HVA. Despite the effects not resulting in notable improvement of symptoms, the study emphasizes the significance of improving targeted approaches and dosage strategies. Nilotinib's development in PD is a prime example of the difficult process of repurposing cancer medications for neurodegenerative diseases, underscoring the difficulties and possibilities of biomarker-guided therapeutic development.

Keywords: Parkinson’s disease, Nilotinib, Abelson tyrosine kinase, DOPAC

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide. It is characterized by the progressive loss of dopaminergic neurons in the substantia nigra and the presence of lewy bodies, which are intracellular inclusions primarily composed of misfolded α-synuclein. PD results in the development of both motor and non-motor symptoms. Common motor symptoms include rigidity, tremor, bradykinesia, gait, and posture alterations. Non-motor symptoms include fatigue, anxiety, mood disorders, and sleep disorders.

Multiple studies have linked an increased activation of cellular Abelson tyrosine kinase (c-Abl) to disease progression in PD. Nilotinib, an oral c-Abl inhibitor, previously approved by the FDA for its use in chronic myeloid leukemia has been shown to have neuroprotective effects in patients with PD. It penetrates the blood-brain barrier (BBB) and stimulates clearance of α-synuclein via autophagy and in doing so prevents the loss of dopaminergic neurons and improves motor symptoms. Homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic Acid (DOPAC) are metabolites of dopamine and are therefore used as CSF markers for dopamine metabolism. Together, α-synuclein, HVA, and DOPAC play a vital role in understanding the neuroprotective effects of nilotinib in PD.

The objective of our review is to evaluate the efficacy of nilotinib in the management of PD using CSF biomarker levels and Unified Parkinson's Disease Rating Scale (UPDRS), as well as its safety profile.

DISCUSSION

Nilotinib has been shown to be a potential disease-modifying agent in PD, through several clinical studies including randomised control trials and open-label extensions. Data shows that nilotinib crosses the BBB, alters biomarker levels in a dose-dependent manner [(5)], and is detectable in the CSF of all dose groups. An increase in CSF levels of HVA was observed in the 150-mg group, while plasma levels of DOPAC were elevated in the 300-mg group suggesting that drug metabolism varies with dosage. While there was an insignificant change in levels of total α-synuclein in CSF at 12 months, the CSF oligomeric/total α-synuclein ratio was reduced in the nilotinib 150-mg group as compared to the placebo group [(3)].

Safety concerns have been a vital part in nilotinib's clinical evaluation in PD management. Both Serious Adverse Effects (SAEs) and Non Serious Adverse Effects (non-SAEs) were more frequent in the nilotinib group compared to the placebo group. There have been mixed reports about the correlation of the dosage of medication and the development of adverse effects. While a few studies [(2)] observed no significant difference between the 150-mg and 300-mg nilotinib groups in comparison with the placebo group, there were more non-SAEs and SAEs observed with nilotinib 150 mg compared with 300 mg in others [(1)]. Overall, these adverse events were attributed to the possibility of pre-existing comorbidities common in the older population, rather than a direct complication caused by nilotinib [(1)]. Most studies surprisingly demonstrated worsening motor scores particularly at 300-mg of nilotinib with comparison to 150-mg. In contrast, another study [(1)] showed better results with 300-mg being more stable than the 150-mg group.

Although nilotinib does seem to possess pharmacological activity relevant to PD pathophysiology, clinical trials have not consistently shown significant improvements in motor symptoms. The safety profile of nilotinib is yet to be fully understood due to varying reports which necessitates further research.

RESULTS

In a 2020 study, a total of 63 patients who completed a 15-month randomized, double-blind, placebo-controlled trial were rerandomized in a 1:1 ratio into a 12-month open-label extension (OLE) study to receive either nilotinib150-mg or 300-mg daily [(1)]. Over these 27 months, the 300-mg group maintained stable UPDRS scores, whereas the 150-mg group worsened. Specifically, UPDRS Part I and Part II remained unchanged at 300- mg but declined at 150-mg. UPDRS Part III was stable in both groups. The combined UPDRS I & II scores significantly favored 300-mg over 150-mg. A total of 9 SAEs occurred in the nilotinib 150-mg group and 4 in the 300-mg group, with no statistically significant difference between groups (P=0.22). In the 150-mg group, one patient was discontinued due to cervical cord compression and another due to esophageal carcinoma. In the 300-mg group, two patients

discontinued one due to non-ST elevation myocardial infarction (NSTEMI) and another was removed by the principal investigator (PI) due to renal failure.

In a 6-month, multicenter, randomized parallel-group, double-blind, placebo-controlled trial of 76 participants [(2)], both doses of nilotinib were tolerable, with 21 (84%), 19 (76%), and 20 participants (77%) completing the study receiving the assigned dose, respectively, for the placebo and 150-mg and 300-mg nilotinib groups (P= .36 and P= .39 for nilotinib, 150-mg and 300-mg, respectively, vs placebo). However, there were more premature withdrawals owing to adverse effects in the nilotinib 300-mg group. Among the 8 participants who withdrew prematurely, one was in the placebo group (due to tremor), two were in the 150-mg group (due to anxiety and an increase in lipase levels), and five were in the 300-mg group (two were due to an increase in lipase, and the others due to arthritis, arrhythmia, and an abnormal ECG). At 6 months, there was an average decrease of 3.4 and 3.6 points in UPDRS-III, as compared to baseline levels in the 150-mg and 300-mg nilotinib groups, respectively. During this time, there was an average decrease of 7 and 11.1 points in UPDRS I-IV in the 150-mg and 300-mg groups, respectively. However, these progressive UPDRS scores returned to baseline levels in all participants by the 36-week follow-up.

A 2022 meta-analysis of three studies [(4)] with a total of 163 patients found that the 300-mg nilotinib group had significantly higher MDS-UPDRS III scores than placebo (95% CI: 0.12 to 0.92; P = 0.01), indicating worsened motor symptoms. No significant differences were observed between the 150-mg group and placebo (95% CI: –0.20 to 0.58), or between the 300-mg and 150-mg groups (95% CI: –0.13 to 0.65). The 300-mg nilotinib group showed significantly lower α-synuclein levels than both the 150-mg group (95% CI: –1.70 to –0.61; P < 0.0001) and placebo (95% CI: –3.38 to –1.84; P < 0.00001). HVA levels showed no significant differences across groups (all P > 0.05). For DOPAC, the 300-mg group had significantly higher levels than placebo (95% CI: 0.12 to 0.92; P = 0.01), while the 150-mg group did not (95% CI: –0.92 to 1.27). Pooled data showed no significant differences in non-serious or serious adverse events between the 150-mg and 300-mg nilotinib groups, or versus placebo. Falls were the most common non-SAE (34% in 150-mg; 25.5% in 300-mg), followed by musculoskeletal disorders (30.9% in 150-mg; 17.2% in 300-mg). SAE incidence was higher for cardiac and gastrointestinal disorders in the 300-mg group, suggesting a dose-related increase. Additionally, incidences of skin and subcutaneous disorder were reported.

In another randomized controlled trial of 300 patients, 75 patients were enrolled post-screening [(3)]. Non-SAEs were reported in all groups, highest being in the nilotinib 150-mg group (71), followed by the placebo group (65) and the least in nilotinib 300-mg group (57), but no significant adverse reactions were noted across the groups (P=0.08). Groups receiving nilotinib 150-mg (4%) and 300-mg (8%), experienced a rare elevation in pancreatic enzymes. SAEs were significantly more frequent in nilotinib 300-mg group [12 (48%)], followed by nilotinib 150-mg group [6 (24%)] and least in placebo group [4 (16%)] with a significant difference (P=0.03). Four of which were cardiovascular in nature with no significant difference (P=0.81) between all three groups and no OTc interval prolongation were noted. Trace amounts of nilotinib were detected in the CSF in the 150-mg (0.94nM) and 300-mg (1.6nM) groups and plasma levels in 150-mg (245.2nM) and 300-mg (299.5nM) groups. At 12 months CSF and plasma levels of DOPAC were significantly increased in both groups as compared to placebo groups. There were no significant differences in α-synuclein and total CSF α-synuclein levels across the groups. However, CSF oligomeric/total α-synuclein ratio was reduced in the nilotinib 150-mg group (33%; 95% CI, 0.0001%-0.0003%) as compared with placebo group. There was a significant increase in CSF

HVA levels in 150-mg group (159.80nM; 90% CI, 7.04-312.60nM; *P*= .04) as compared with placebo at 12 months) and insignificant increase (86.64nM; 90% CI, –104.6 to 277.9nM) in the nilotinib 300-mg group. No differences were observed in MDS-UPDRS-I within and between all study groups. At 12 months total MDS-UPDRS I-III (2.47) and I-IV (2.13) scores changed in the placebo group, but no changes in nilotinib groups were observed. However, the nilotinib 150-mg (–2.82 points, 95% CI, –4.75 to –0.89 points) group showed significant improvement in MDS-UPDRS-III score at 15 months but no significant differences were observed in MDS-UPDRS-IV.

CONCLUSION

Originally developed as a chemotherapeutic agent, nilotinib has exhibited its potential for repurposing in PD. Nilotinib has been associated with reductions in neurodegenerative protein markers such as α-synuclein and increased levels of dopamine metabolites (DOPAC and HVA) in CSF indicating its ability to cross the BBB. Despite its proven beneficial effects, the high incidence of adverse events warrants a careful evaluation of nilotinib's risk-benefit profile. While nilotinib, in its present form, may not fulfil the promise of being a disease-modifying therapy, it advances the search for a novel mechanism-based treatment option for PD. Further studies are needed to fully explore other possible mechanisms, optimize dosing strategies, and identify biomarkers predictive of response.

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