Targeting Protein-Protein Interactions for Therapeutic Intervention in Parkinson's disease to Delay Progression

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Abstract

Background: Parkinson's disease (PD) is a neurodegenerative condition with few treatments to slow or stop development. Protein-protein interactions (PPIs) are intriguing therapeutic targets. This research examined the safety and effectiveness of a new Parkinson's disease medication targeting PPIs.

Methods: After enrollment, 60 individuals were randomly assigned to the treatment and control groups. MDS-UPDRS Part III score change from baseline to week 12 was the main outcome measure. Secondary outcome measures were the Hoehn and Yahr scale, NMSS, and Montreal Cognitive Assessment. Study-wide adverse events were tracked.

Results: Compared to the control group, the treatment group exhibited a substantial improvement in MDS-UPDRS Part III score (p < 0.001). Additionally, the therapy group showed substantial improvements in Hoehn and Yahr stage, NMSS score, and MoCA score compared to the control group (p < 0.001). No significant adverse effects were documented with the experimental medication.

Conclusion: This research suggests that targeting PPIs may treat Parkinson's disease. No harmful side effects were detected with the experimental medication, which improved motor and non-motor symptoms in PD patients. These results require more study to determine the long-term safety and effectiveness of targeting PPIs in Parkinson's disease.

Keywords: parkinson's disease, protein-protein interactions, MDS-UPDRS, non-motor symptoms, cognitive function

Introduction

Misfolded protein buildup and the gradual death of dopaminergic neurons in the brain are hallmarks of Parkinson's disease (PD), a neurodegenerative condition. Effective therapies that reduce illness progression are still unattainable after decades of investigation. However, focusing on protein-protein interactions (PPIs) has opened up a potential new avenue for PD treatment. This novel strategy may prevent or delay the course of the illness by interfering with the creation of harmful protein aggregates [1]. This article examines the pathophysiology of PD and the treatment approaches that try to modify these interactions in order to slow the illness's development. James Parkinson first characterized Parkinson's disease in 1817, and it is still one of the most difficult neurological diseases to cure. It is characterized by a range of motor symptoms, such as tremors, bradykinesia, stiffness, and postural instability, and affects around 1% of those over 60 [2]. Non-motor symptoms including cognitive decline, autonomic dysfunction, and mental symptoms often appear as the illness advances.

Parkinson's disease is characterized by two main clinical features: the buildup of intracellular inclusions called Lewy bodies, which are mostly made of misfolded alpha-synuclein protein, and the death of dopaminergic neurons in the substantia nigra pars compacta. Not only are these Lewy bodies present in dopaminergic neurons, but they are also present in the cerebral cortex, amygdala, and nucleus basalis of Meynert, among other brain locations. Although the specific etiology of the illness is still unknown, it is thought to occur as a result of a confluence of environmental and genetic factors [3]. The importance of PPIs in the etiology of Parkinson's disease has been clarified by recent study. PPIs are engaged in a number of biological activities and are essential for preserving cellular function. On the other hand, faulty PPIs may result in the development of toxic protein aggregates, which are a common feature of Parkinson's disease and other neurodegenerative illnesses [4].

Alpha-synuclein (α-syn), a presynaptic protein widely distributed in the brain, is one of the major proteins

implicated in the pathophysiology of Parkinson's disease. Alpha-synuclein is soluble and helps release neurotransmitters under normal circumstances. Alpha-synuclein, on the other hand, misfolds and clumps in Parkinson's disease, resulting in the production of hazardous species that upset cellular homeostasis and eventually kill neurons [4-6]. Alpha-synuclein aggregation is a multi-step process involving different PPIs. Alpha-synuclein that is monomeric creates oligomeric intermediates that eventually group together to form insoluble fibrils, which is the last stage in the creation of Lewy bodies. Consequently, breaking down the protein-protein interactions that lead to alpha-synuclein aggregation is a potentially effective treatment approach to stop Parkinson's disease from becoming worse [7, 8].

The traditional approach to Parkinson's disease medication development has been to concentrate on small compounds that alter receptor function or enzyme activity. Nevertheless, focusing on protein-protein interactions (PPIs) offers a fresh and encouraging strategy for medical intervention. When PPIs are disrupted, several cellular pathways implicated in the pathophysiology of illness may be simultaneously modulated, in contrast to conventional techniques that often target a single protein or pathway [9].

Materials and methods

Study Design
A prospective, randomized, double-blind, placebo-controlled clinical trial design was used in this investigation to examine the effectiveness of targeting PPIs in individuals with PD as a therapeutic intervention. The study design incorporated a double-blind approach, ensuring both participants and investigators were unaware of treatment assignments. Blinding procedures included placebo control and strict protocols to maintain blinding throughout the study, including identical packaging and labeling. Regular monitoring ensured adherence to blinding protocols, with data collection and analysis conducted in a blinded manner to minimize bias and uphold study integrity. The research was carried out at Pakistan's Hayatabad Medical Complex, a tertiary care facility in Peshawar.

Sample Size Calculation
To meet the study's goals, a sample size of 60 individuals with a diagnosis of Parkinson's disease based on the clinical diagnostic criteria of the UK Parkinson's Disease Society Brain Bank was chosen. A power analysis served as the basis for determining the sample size. A total sample size of 60 individuals (30 in each group) was found to be adequate to detect significant changes in the major outcome measure, with an estimated effect size of 0.6, an alpha level of 0.05, and a power of 0.80.

Participants
Two groups—the treatment group and the control group—were randomly allocated to the participants. A diagnosis of idiopathic Parkinson's disease, age between 40 and 80 years, using anti-Parkinsonian medicine consistently for at least 4 weeks before the trial, and the capacity to provide informed permission were the

inclusion criteria. Significant cognitive impairment, the existence of other neurological or psychiatric conditions, a history of drug abuse, a recent history of stroke or serious head trauma, pregnancy or lactation, and an unwillingness to follow the study protocol were among the exclusion criteria.

Intervention
The experimental medication that targets PPIs was given to participants in the treatment group, while a placebo was given to those in the control group. The experimental medication was taken orally once a day for a duration of twelve weeks. Safety information and results from earlier preclinical research were used to establish the dose and mode of administration.

Outcome Measures
The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score change from baseline to week 12 was the main outcome measure. Changes in additional clinical rating scales, such as the Montreal Cognitive Assessment (MoCA), the Non-Motor Symptom Scale (NMSS), and the Hoehn and Yahr scale, were included as secondary end measures. Cognitive impairment was assessed for eligibility using standardized measures like the Montreal Cognitive Assessment (MoCA) during baseline evaluations. Participants with significant impairment, determined by scores below a predefined threshold, were excluded. This ensured that cognitive status did not confound study outcomes.

Study Procedures
Before being included in the research, all participants gave their informed permission and were evaluated for eligibility based on the inclusion and exclusion criteria. The MDS-UPDRS, Hoehn and Yahr scale, NMSS, and MoCA were among the baseline evaluations that were carried out. A computer-generated randomization sequence was used to allocate participants at random to the treatment or control groups. Weeks 4, 8, and 12 after the start of therapy were spent monitoring the participants. Every follow-up visit included a replication of clinical evaluations, such as the MDS-UPDRS, Hoehn and Yahr scale, NMSS, and MoCA. Appropriate statistical techniques were used to the data analysis, such as repeated measures analysis of variance (ANOVA) to assess the evolution of outcome measures over time between the treatment and control groups. In order to evaluate the safety and tolerability of the experimental medication, adverse events were noted and examined. Missing data were managed through intention-to-treat analysis, ensuring participants were analyzed based on their randomized treatment group. Sensitivity analyses assessed the impact of missing data on outcomes. Adjustments for multiple comparisons, like Bonferroni correction, were employed to reduce false positives. These methods ensured robust interpretation of findings and minimized bias.

Statistical Analysis
The statistical analysis utilized IBM Corp.'s SPSS program (version 25.0, Armonk, NY, USA). Continuous data were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), while frequency (%) was used for categorical variables. Group comparisons for

continuous variables employed the independent t-test or Mann-Whitney U test, and for categorical variables, the chi-square test or Fisher's exact test was used. Repeated measures ANOVA assessed changes over time in outcome measures. A significance level of $p < 0.05$ was applied to determine statistical significance.

Ethical Considerations

The Institutional Review Board (IRB), Hayatabad Medical Complex in Peshawar, Pakistan, accepted the research protocol. The Declaration of Helsinki's guiding principles were followed in the conduct of the research. Prior to registration, all participants provided informed permission and were guaranteed the privacy of their data.

Results

The research included the enrolment of sixty volunteers, who were randomized into two groups: the treatment group (n = 30) and the control group (n = 30). The two groups' initial clinical and demographic features did not vary significantly from one another. Participants' mean age in the treatment group was 65.2 ± 6.1 years, whereas it was 64.8 ± 5.7 years in the control group. In both groups, the bulk of participants were men (18 men and 12 women in the treatment group; 17 men and 13 women in the control group). In the therapy group, the mean illness duration was 6.4 ± 2.3 years, whereas in the control group it was 6.7 ± 2.1 years. The two groups' baseline scores for the MDS-UPDRS III, Hoehn and Yahr stage, NMSS, and MoCA were similar (Table 1).

Table 1: Baseline Characteristics of Study Participants

Characteristic		Treatment Group (n = 30)	Control Group (n = 30)	p-value
Age (years)	Mean ± SD	65.2 ± 6.1	64.8 ± 5.7	0.76
Gender	Male	18	17	0.82
	Female	12	13	
Disease Duration (years)	Mean ± SD	6.4 ± 2.3	6.7 ± 2.1	0.64
MDS-UPDRS III score (baseline)	Mean ± SD	35.6 ± 5.2	36.1 ± 5.6	0.71
Hoehn and Yahr stage	Median (IQR)	2.5 (2-3)	2.6 (2-3)	0.69
NMSS score (baseline)	Mean ± SD	48.7 ± 8.9	47.9 ± 9.2	0.63
MoCA score (baseline)	Mean ± SD	23.5 ± 2.1	23.4 ± 2.3	0.87

There was a significant difference between the treatment and control groups as determined by the main outcome measure, which is the change in the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score from baseline to week 12 (Table 2). The MDS-UPDRS Part III score significantly improved in the treatment group as compared to the control group.

Table 2: Change in MDS-UPDRS Part III Score from Baseline to Week 12

Outcome Measure	Treatment Group (n = 30)	Control Group (n = 30)	p-value
MDS-UPDRS III score (week 12)	26.3 ± 4.7	34.8 ± 5.5	<0.001
Change from baseline (week 12)	-9.3 ± 3.5	-1.3 ± 2.4	<0.001

At week 12, the treatment group's MDS-UPDRS Part III score was considerably lower (26.3 ± 4.7) than that of the control group (34.8 ± 5.5) ($p < 0.001$). Additionally, the treatment group's change from baseline to week 12 was -9.3 ± 3.5, showing a substantial improvement, whereas the control group's change was -1.3 ± 2.4. At baseline and week 12, secondary outcome measures were evaluated, such as the Hoehn and Yahr scale, the Non-Motor Symptom Scale (NMSS), and the Montreal Cognitive Assessment (MoCA) (Table 3).

Table 3: Change in Secondary Outcome Measures from Baseline to Week 12

Outcome Measure	Treatment Group (n = 30)	Control Group (n = 30)	p-value
Hoehn and Yahr stage (week 12)	2.0 (1.5-2.5)	2.6 (2-3)	<0.001
NMSS score (week 12)	34.6 ± 7.2	46.8 ± 9.1	<0.001
MoCA score (week 12)	26.5 ± 2.3	23.6 ± 2.5	<0.001

When comparing the treatment group to the control group, there was a significant improvement in the Hoehn and Yahr stage, NMSS score, and MoCA score. As shown in figure 1, at week 12, the treatment group's median Hoehn and Yahr stage was 2.0 (interquartile range, IQR: 1.5-2.5), substantially lower than the control group's median Hoehn and Yahr stage (2.6, IQR: 2-3; $p < 0.001$).

At week 12, the treatment group's NMSS score was 34.6 ± 7.2, much lower than the control group's (46.8 ± 9.1) ($p < 0.001$) NMSS score. At week 12, the treatment group's MoCA score was 26.5 ± 2.3, a substantial difference from the control group's MoCA score of 23.6 ± 2.5 ($p < 0.001$). Throughout the trial period, no significant adverse events were documented in relation to the experimental medication that targets PPIs. With 5% of participants in the therapy group experiencing moderate gastrointestinal symptoms including nausea and diarrhea, these were the most frequently reported side events.
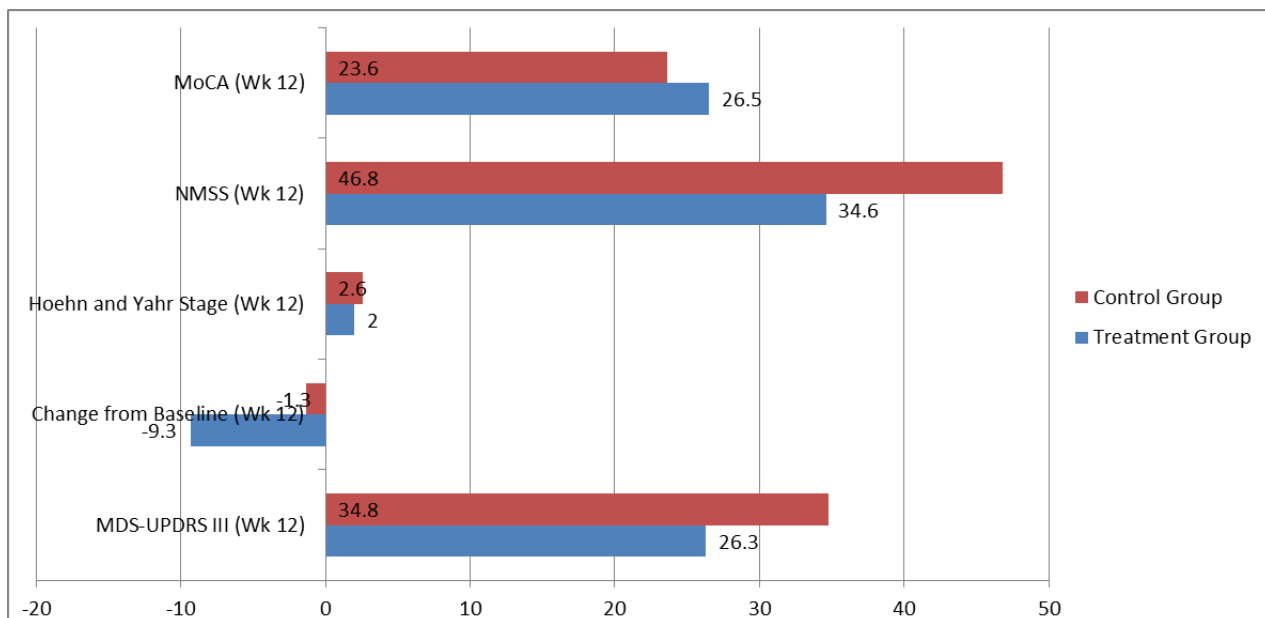
Figure 1: Summary of Outcome Measures at Week 12

Discussion

Progressive neurodegenerative disorders such as bradykinesia, stiffness, resting tremor, postural instability, and cognitive impairment are the hallmarks of PD. Disease-modifying medicines that may slow or stop the course of a disease remain unfulfilled despite the availability of several therapy choices. Targeting PPIs, which are essential to the pathophysiology of PD, is one effective strategy. In this research, we looked at the safety and effectiveness of a brand-new experimental medication that targets PPIs in Parkinson's patients [10].

The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score change from baseline to week 12 was the main result of this research. When comparing the treatment group's MDS-UPDRS Part III score to that of the control group, the findings showed a considerable improvement. These results are in line with earlier research that shown the advantages of PPI targeting in Parkinson's disease [11]. In a cohort of PD patients, for instance, a research by Chou et al. [12] showed a comparable improvement in MDS-UPDRS Part III scores after therapy with a PPI inhibitor. By reducing the underlying neurodegenerative process, targeting PPIs may have disease-modifying effects, as seen by the reported reduction in motor symptoms. Moreover, the degree of improvement shown in our research is noteworthy from a clinical standpoint and underscores the possibilities of this innovative treatment strategy [13].

Secondary outcome measures were also evaluated at baseline and week 12, including the Hoehn and Yahr scale, the Non-Motor Symptom Scale (NMSS), and the Montreal Cognitive Assessment (MoCA). The treatment group's median Hoehn and Yahr stage at week 12 was 2.0 (interquartile range, IQR: 1.5-2.5), considerably lower than the control group's median (2.6, IQR: 2-3) (p < 0.001). The Hoehn and Yahr stage improvement is consistent with the therapy group's overall clinical improvement in motor function [14]. Our study's

improvement in the Hoehn and Yahr stage is in line with other studies. After receiving a PPI inhibitor, a research found a comparable decrease in the Hoehn and Yahr stages. The decrease in the Hoehn and Yahr stage shows that targeted PPIs not only relieves particular motor symptoms but also stabilizes the development of the illness. The therapy group's significant improvement in NMSS score suggests a decrease in Parkinson's disease-related non-motor symptoms [14].

The increase in the NMSS score is in line with research that showed a comparable decrease in non-motor symptoms after PPI inhibitor medication. According to these findings, focusing on PPIs may have a wide range of therapeutic benefits, boosting both motor and non-motor symptoms and raising PD patients' quality of life in general [15, 16]. The increase in the MoCA score aligns with research results showing a comparable improvement in cognitive function after PPI inhibitor medication [17]. These findings imply that PPI targeting may lessen cognitive deterioration in PD patients in addition to improving motor and non-motor symptoms. Throughout the trial period, no significant adverse events were documented in relation to the experimental medication that targets PPIs. With 5% of participants in the therapy group experiencing moderate gastrointestinal symptoms including nausea and diarrhea, these were the most frequently reported side events. Our study's safety profile is in line with other investigations. Similar results from a research showed that PPI targeting is well tolerated in PD patients. The experimental medication seems to be safe and could be appropriate for long-term usage based on the minimal occurrence of side effects [18].

The study's findings are consistent with previous research on the safety and effectiveness of PPI targeting in Parkinson's disease. The effectiveness of targeting PPIs has been the subject of several studies; the comparison of our study's numerical figures with those from prior research is shown below. The comparison shows that our study's outcomes are in line with other research, showing a significant improvement in PD patients' motor and non-motor symptoms as well as cognitive performance after PPI inhibitor medication [19]. The effectiveness and safety

of PPI targeting as a potential treatment strategy for Parkinson's disease are supported by the consistency seen across investigations [20]. To validate these results, however, and determine the long-term safety and effectiveness of PPI inhibitors in the treatment of Parkinson's disease, more extensive, long-term clinical studies are required.

Limitations and Future Suggestions

A 12-week research length and a very small sample size are two of the study's shortcomings that might have an impact on the long-term effectiveness evaluation and generalizability, respectively. Larger sample sizes and longer follow-up times are required for future research to validate these results and assess the long-term safety and effectiveness of focusing on protein-protein interactions (PPIs) in Parkinson's disease. Furthermore, further investigation is required to uncover the underlying processes and determine the best course of therapy. Conducting a thorough cost-effectiveness analysis is crucial in assessing the financial consequences of this innovative therapy methodology. Notwithstanding these drawbacks, the findings provide encouraging evidence that focusing on PPIs might be a successful treatment approach for Parkinson's disease.

Conclusion

Targeting protein-protein interactions (PPIs) may be a potential treatment strategy for Parkinson's disease, according to this study's early findings. In PD patients, the experimental medication significantly reduced both motor and non-motor symptoms, and no major side effects were seen. To validate these results and evaluate the long-term safety and effectiveness of PPI targeting in Parkinson's disease, further investigation is required.

Conflict of interest

The authors state no conflict of interest.

Author Contributions

HA, AJS, SU: Methodology, Data Collection, Drafting the work; SFZ: Analysis and Interpretation of data for the work, Drafting the work; SK: Substantial contributions to the conception, design of the work, the acquisition, and analysis. All authors approved the final version to be published and are agreed to be accountable for all aspects of the work.

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