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Immunomodulation as a Treatment for Parkinson's Disease in Current Trials: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Immunomodulatory drugs and immunotherapies are being evaluated in clinical trials for the treatment of neuroinflammation, as the latter is an essential mechanism for the development and progression of Parkinson's disease. **Objective:** The objective of the study is to review recent evidence on the evaluation of immunomodulators in randomized controlled clinical trials measuring improvement of motor symptoms. **Methods:** A meta-analysis of Movement Disorder Society-Unified Parkinson's disease Rating Scale (MDS-UPDRS III) scores extracted from seven articles selected after an online search of PubMed, Cochrane Library, and Clarivate's Web of Science for randomized controlled clinical trials published between 2000 and July 2023 was performed. The selected articles reported clinical trials evaluating the effects of specific immunomodulators or treatments with known effects on the immune system and inflammation. MDS-UPDRS III scores were reported in these studies, and the results of the placebo groups were compared with those of the treatment groups. **Results:** A total of 590 patients treated with immunomodulators and 622 patients treated with placebo were included. A test for heterogeneity yielded an I^2 value > 50%. The mean standard difference for change in MDS-UPDR III score was −0.46 (CI [95%] = −0.90 - −0.02, p < 0.01). No significant differences were found in the change in mean MDS-UPDR III score between the treatment and placebo groups; however, two studies showed a trend toward separation from the mean. **Conclusion:** The immunomodulatory treatments included in this study showed no efficacy in improving motor symptoms in Parkinson's disease patients. Further clinical trials with larger patient populations are needed. (REV INVEST CLIN. 2024;76(3):159-69)

Keywords: Parkinson's disease. Immunomodulation. Meta-analysis. Clinical trial. Treatment efficacy.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease associated with aging and the fastest-growing neurodegenerative disease. It is expected that there will be 12 million cases by 2040[1]. Worldwide, more than 8.5 million people were reported to have PD in 2019[2,3]. This pathology is characterized by movement disorders due to the loss of dopaminergic neurons and degeneration of the substantia nigra pars compacta[4]. The main pathognomonic symptoms are tremor, bradykinesia, rigidity, and postural instability. However, non-motor symptoms such as depression, cognitive changes, neuropsychiatric manifestations,

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constipation, and fatigue may precede motor symptoms by up to 20 years[5,6]. The therapeutic strategy to be used depends on the age of the patient, the progression of the disease, the severity of the symptoms, and the risk/benefit assessment of the chosen treatment[7]. Carbidopa/levodopa, dopaminergic agonists, and monoamine oxidase B inhibitors are the most widely used drugs as initial therapy; however, these treatments are palliative and there is no cure or drug to halt the progression of neurodegeneration[8,9]. Recently, efforts have been made to investigate therapies that focus on reducing neuroinflammation and promoting neuroprotection. Cell therapy for neuronal regeneration with pluripotent neural cell-inducing mesenchymal stem cells and mesenchymal neural progenitor cells accounted for 12.2% of all phase-I clinical trials in 2021, whereas immunotherapy (anti-alpha-synuclein antibodies or alpha-synuclein immunogenic peptides) to prevent neurotoxicity accounted for 10.2% of trials[10].

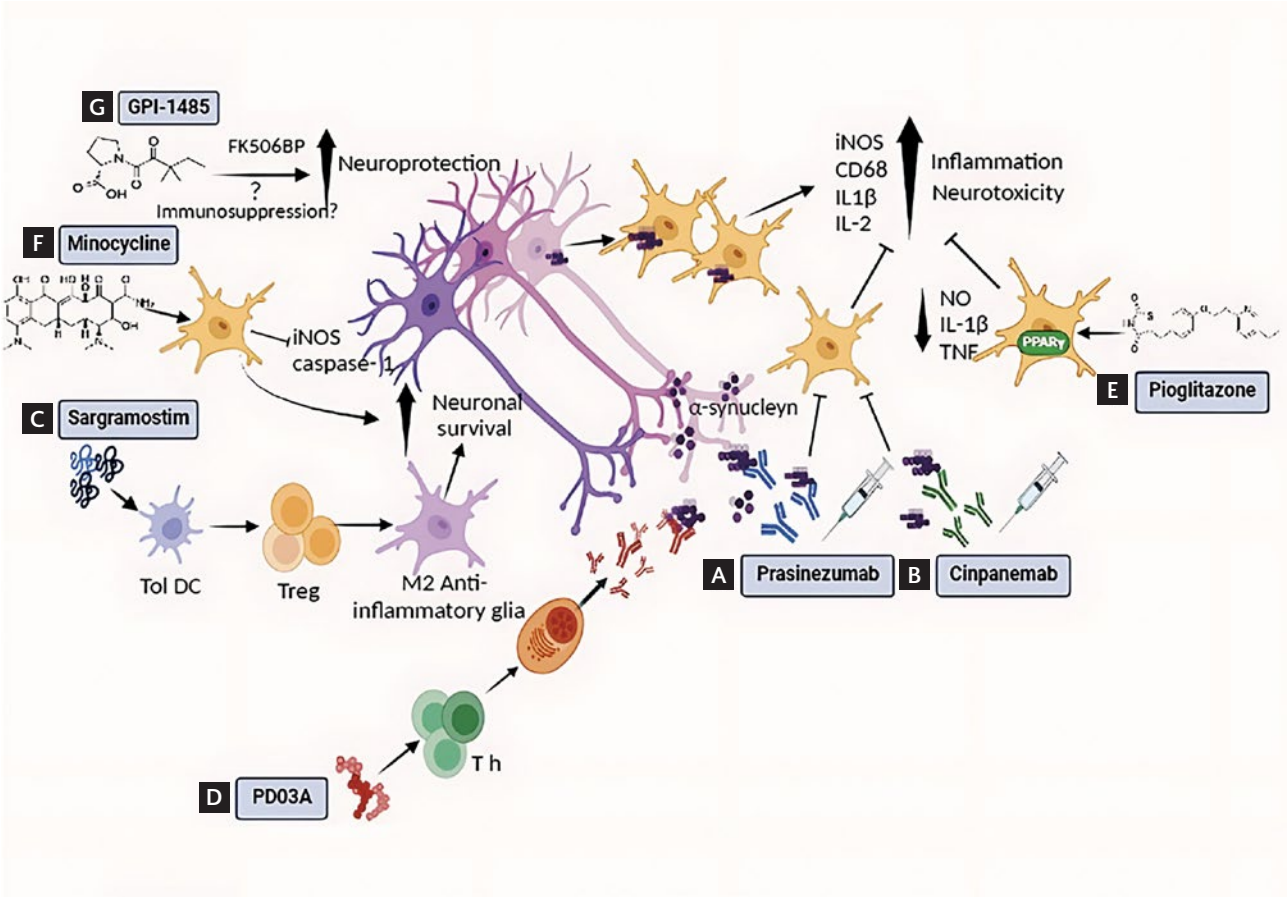
Neuroinflammation, the activation of an inflammatory immune response within the brain or spinal cord, is an active area of research related to central nervous system (CNS) disorders. This process is mediated by both soluble and cellular factors secreted by the CNS and peripheral tissues. Soluble factors include proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor (TNF), and interleukin-6 (IL-6); chemokines such as CCL2 and CXCL1; and molecules such as prostaglandins and nitric oxide (NO)[11]. High serum levels of TNF have been linked to increased severity of depression, fatigue, and cognitive problems[12]. Cellular factors involved in neuroinflammation include microglial cells, astrocytes, endothelial cells, and perivascular macrophages[13]. These cells detect signals such as an accumulation of modified alpha-synuclein, increased oxidative stress, neuron damage, and secrete pro-inflammatory mediators (IL-1β, IL-6, TNF, and NO) that aggravate the process. The adaptive immune response is also activated, with cells migrating into the CNS and exacerbating neurodegeneration[14].

Immunomodulatory therapy aims to regulate the neurotoxic inflammatory response by reducing it or preventing an exacerbated neuroinflammatory phenomenon. It has been described that PD patients exhibit decreased counts of immunosuppressive regulatory T cells and increased counts of effector T cells, correlating with the severity of clinical manifestations[15]. Immunomodulatory therapy aimed at boosting regulatory T cells could modulate the immune response in these patients and thereby have a beneficial effect on symptoms and/or slow disease progression. Studies of this therapeutic approach range from passive immunization with anti-alpha-synuclein antibodies to the use of soluble factors such as vasoactive intestinal peptide or granulocyte-macrophage colony-stimulating factor (GM-CSF). Similarly, therapeutic agents have been tested in animal models with results that suggest they may be successful in humans. For example, in mice, the GM-CSF produces increased levels of CD4 + CD25 + FOXP3 + regulatory T cells, which inhibit the proliferation of CD3/CD28-activated effector CD4 + CD25 T-cells. These regulatory cells exerted a neuroprotective effect when transfected into MPTP-treated mice. In a rat model of human alpha-synuclein overexpression, regulatory T cells generated by elevated plasma levels of GM-CSF increased the survival rate of tyrosine hydroxylase-positive (TH+) dopaminergic neurons[16]. Similarly, Alzheimer's disease patients treated with sargramostim (GM-CSF) 250 μg/m^2/day 5 times/week for 3 weeks showed altered immune profiles with increased monocyte, lymphocyte, and neutrophil counts, as well as IL-10, IL-6, and TNF secretion, and improved plasma biomarkers of cognition and neuropathy without significant adverse effects[17].

Therefore, the administration of immunomodulators could help control neuroinflammation in PD (Fig. 1). Immunomodulators and immunotherapy could be used in different approaches. For example, pioglitazone, a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist used to treat type 2 diabetes by reducing insulin resistance, inhibits microglial activation and reduces NO and proinflammatory cytokine levels in a rat model of PD[18]. On the other hand, cinpanemab and prasinezumab, monoclonal antibodies of human origin that binds to alpha-synuclein aggregates, have been shown to reduce motor impairment[19].

In addition to evaluating the effect of immunomodulators and exploring their mechanism of action, the current studies in animal models and clinical trials assess the risks and adverse effects of these drugs in patients. The objective of this meta-analysis is to review recent evidence on the evaluation of

Figure 1. Proposed mechanism of action for Parkinson's disease (PD) treatments included in this meta-analysis. Several therapeutic strategies are used to modulate neuroinflammation. **A:** prasinezumab and cinpanemab are humanized monoclonal antibodies that selectively bind alpha-synuclein. In murine models, prasinezumab reduced the propagation, aggregation, and accumulation of alpha-synuclein by binding to its C-terminal residue, preventing its transport to other neurons and microglial cells and improving protein clearance. **B:** cinpanemab selectively binds to extracellular alpha-synuclein. Both therapies could prevent neurotoxicity and inflammation following glial activation. However, this mechanism has not been extensively studied in animals and not at all in humans; it is possible that the presence of the alpha-synuclein-antibody complex could activate the immune response. **C:** dysfunction of the innate and adaptive immune response in PD is characterized by the production of proinflammatory cytokines, proinflammatory glia, presence of effector T cells, and decreased Treg cell counts. Sargramostim is a recombinant human granulocyte-macrophage colony-stimulating factor that increases CD4 + CD127loCD25hi Treg cell expression and induces tolerogenic dendritic cells in humans. By regulating the suppressor response, sargramostim could modulate glia toward an M2 phenotype, attenuating neuroinflammation and promoting neuron survival and neuroprotection, as observed in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and in patients with Alzheimer's disease, stroke, and traumatic brain injury[20-23]. **D:** PD03A is a 10-amino-acid peptide designed to mimic an epitope of the C-terminal region of alpha-synuclein. The peptide is conjugated to a Th-cell antigen to elicit a long-lasting antigenic response. PD03A is a B-cell epitope that promotes a significant humoral response that neutralizes extracellular alpha-synuclein and prevents glial activation[24]. **E:** pioglitazone is an antidiabetic thiazolidinedione (TZD), a synthetic ligand of PPAR-γ. TZDs have been shown to regulate inflammation by decreasing IL-1β and TNF production by macrophages and microglia; in mice, pioglitazone inhibited nitric oxide (NO) production. In neuron-microglia cocultures, pioglitazone inhibited microglial activation and reduced NO production[25-27]. **F:** tetracyclines such as minocycline have shown pharmacological effects in addition to antibiotic activity, such as inhibition of superoxide production in neutrophils and iNOS expression in macrophages. In a mouse MPTP model of PD, minocycline prevented dopaminergic neuron degeneration and loss of striatal dopamine. In primary cultures of astrocytes and microglial cells, treatment decreased the expression of iNOS and caspase 1 and reduced the expression of caspase 1 in neurons. However, the mechanism has not been studied in humans[28,29]. **G:** finally, GPI-1485 is a tacrolimus-derived neuroimmunophilin ligand (NIL) that has demonstrated neuroprotective activity by reversing neurodegeneration and preventing cell death. NILs bind to a group of proteins called FK506-binding proteins, which are involved in the regulation of glucocorticoid receptors, heat shock proteins, and, in immune cells, the inhibition of the expression of cytokines that alter calcineurin. Exactly how NILs act in models of Alzheimer's disease, PD, and trauma-induced neuropathies is unclear, and there is some doubt as to whether such an effect is due to immunosuppression or immune alterations, as no immune cells have been identified as targets of GPI-1485, and NILs do not appear to affect calcineurin[30-32].



immunomodulators in randomized controlled clinical trials measuring the improvement of motor symptoms in PD patients.

METHODS

Search strategy

An online search of PubMed, the Cochrane Library, and Clarivate Web of Science was conducted for randomized controlled clinical trials published between 2000 and July 2023. Selected articles reported on clinical trials evaluating the effects of specific immunomodulators or treatments with known effects on the immune system and inflammation. The keywords used were "PD," "immunomodulation," and "PD immunotherapy." No restrictions were placed on country, population, region, or publication status.

Selection criteria

Randomized, controlled trials comparing the efficacy of immunomodulatory treatments with placebo were included. Interventions were limited to trials involving the administration of immunomodulatory treatment and placebo in patients with PD. All participants included were adult male and female patients diagnosed with PD. The change in score in the Movement Disorder Society-Unified PD Rating Scale (MDS-UPDR III) between patients receiving immunomodulatory treatment or placebo was used for comparison. Therefore, the mean change in MDS-UPDR III score between the placebo and treatment groups was chosen as the outcome variable.

Inclusion/exclusion criteria

All selected articles were randomized controlled clinical trials evaluating immunomodulatory treatments or treatments with some effect on the immune system and inflammation. Conventional symptomatic treatments were excluded. All included studies compared placebo groups with treatment groups and reported MDS-UPDRS III scores and adverse events. Studies that used a different measure or had incomplete data on MDS-UPDRS III scores (e.g., did not report baseline or endpoint scores) were excluded. Studies in healthy subjects and studies without placebo groups were also excluded, as the aim of this paper was to evaluate the effects of treatment in PD patients by comparing placebo with immunomodulatory treatment. Studies published before 2000 were excluded, and only studies published between 2000 and July 2023 were considered for inclusion.

Data extraction

The following data were retrieved from each study: first author and publication year, treatment and dose, number of subjects in placebo and treatment groups, patient demographics, treatment duration, MDS-UPDRS III scores, and the most common adverse events (Table 1).

Two investigators independently reviewed the included studies and identified, extracted, and verified the relevant data. Changes in MDS-UPDRS III scores were obtained directly from the results section of the included studies or calculated if not reported. Changes in the score for each study were calculated by subtracting the baseline score from the final score at the end of treatment. If the final score was less than or equal to the baseline score, this was considered an improvement. For studies with MDS-UPDRS III scores reported as a graph, the WebPlotDigitizer tool (https://automeris.io/WebPlotDigitizer/) was used to calculate the change and standard deviation.

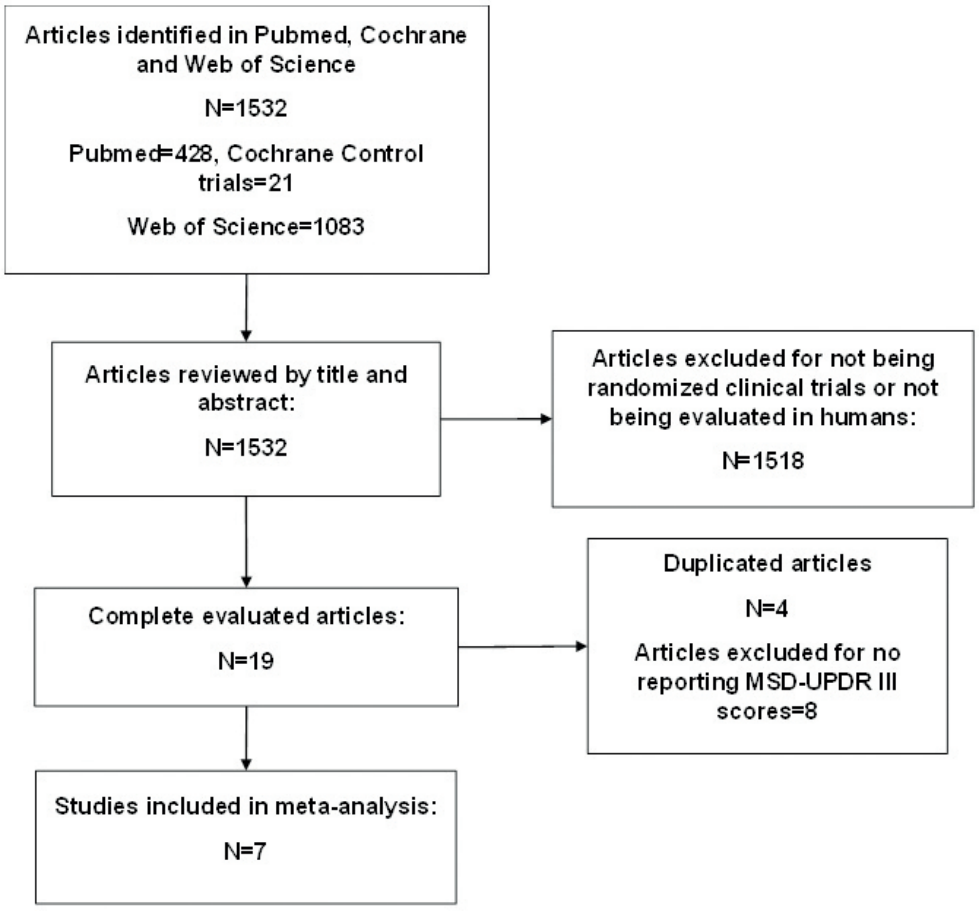
Statistical analysis

Meta-analysis was performed using the R language. Heterogeneity was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating high heterogeneity. When high heterogeneity was observed, a random effects model was used to perform the meta-analysis. The Cochrane Risk of Bias Tool for Randomized Trials (RoB 2) was used to assess the methodological quality and risk of bias of the trials included in the meta-analysis. This tool assesses the presence of bias in five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported outcomes. Each domain was rated as low risk of bias, high risk of bias, or some concern. To assess publication bias, a funnel plot was constructed, and an Egger regression test was performed to assess asymmetry. Finally, a sensitivity analysis was performed by replicating the results of the meta-analysis after excluding one of the studies included in each step to determine the influence of each study on the overall effect estimate.

Table 1. Demographic and basic characteristics of included patients

Study year	Intervention	*N* Placebo	Dose	*N* treatment	Sex (M/F)	Mean age (SD)	Duration	Score change MDS-UPDRS III Placebo/ experimental (SD)	Most common adverse events
Lang et al. 2022	Cinpanemab	53	250 mg 1250 mg 3500 mg	29 58 51	250/107	60.1 (9.0)	52 week	6.1 (2.1)/ 6.7 (2.8) 6.8 (2.1) 6.2 (2.2)	Headache, nasopharyngitis
Pagano et al., 2022.	Prasinezumab (PRX 002)	76	1500 mg 4500 mg	74 73	213/103	61.0	52 week	5.6 (0.9)/ 3.7 (0.9)/ 4.6 (0.9)	Infusion reactions, nasopharyngitis, back pain, headache
Poewe et al., 2021	PD03A	11	15 μg 75 μg	12 12	22/14	58.3	52 week	1.2 (7.1)/ 3.0 (6.5) 0.2 (7.0)	Injection site pain, myalgia
Gendelman et al., 2017	Sargramostim	9	6 μg/kg/day	5	16/4	64 (7)	56 days	4.1 (4.7)/ −5.7 (2.2)	Injection site reaction, abnormal WBC counts, pain in upper torso and extremities
NET-PD FS-ZONE Investigators, 2015.	Pioglitazone	71	15 mg 45 mg	72 67	148/53	59.7	44 week	3.86 (1.39)/ 3.12 (1.33) 3.1 (1.81)	Increased creatinine phosphokinase, edema
NET-PD FS-ZONE Investigators, 2006.	Minocycline	67	200 mg	66	39/59	62.3 (9.1)	12 month	5.34 (6.82)/ 3.98 (5.92)	Nausea, dizziness, respiratory symptoms
NET-PD FS-ZONE Investigators, 2006.	GPI-1485	71	4000 mg	71	96/46	61.0 (9.03)	12 month	5.34 (7.25)/ 3.79 (6.16)	Nausea, joint pain, diarrhea

Figure 2. Literature screening flow chart.



RESULTS

Initially, 1532 articles were found with the keywords used (Fig. 2). After reviewing them by title and abstract, 1518 studies were excluded, most of them for not being clinical trials. Next, 19 studies were reviewed; 8 were excluded for not reporting MDS-UPDR III scores; and 4 were replicated. Finally, seven studies were selected for meta-analysis. These trials tested different immunomodulatory treatments: cinpanemab, prasinezumab (PRX 002), sargramostim (GM-CSF), PD03A, pioglitazone, minocycline, and GPI-1485. The baseline demographic and clinical characteristics of the patients are shown in table 1. In each study, the placebo groups were compared to the treatment groups. Subjects in all groups were patients with early-stage PD, with or without background treatment (levodopa, dopaminergic agonists or MAO-B inhibitors, or combinations).

Risk of bias in included studies

The methodological quality of each study included in the meta-analysis was assessed by the risk of bias in five different domains according to the Cochrane Randomized Trials Tool. Most studies had a low risk of bias, indicating that the included studies were of good methodological quality (Supplementary Fig. 1).

Meta-analysis results

A total of 1212 patients were included in the meta-analysis: 590 patients were treated with immunomodulators and 622 patients received a placebo. Due to the high heterogeneity of the studies (I^2 = 91%, $p < 0.01$), a random effects model was used (Fig. 3). The mean standard difference for change in MDS-UPDR III score was −0.46 (CI [95%] = −0.90 - −0.02, $p < 0.01$). These results show no significant differences

Figure 3. Forest plot for the meta-analysis of change in Movement Disorder Society-Unified Parkinson's disease Rating Scale-III score for placebo versus treatment groups. The number of patients in each group is shown in the "Total" column, and the mean change in score for placebo and treatment groups is shown in the "Mean" column. The first author or investigation group, the year of publication, and the doses administered are shown in the "study" column. Doses are given because multiple doses were tested in the same drug trial.

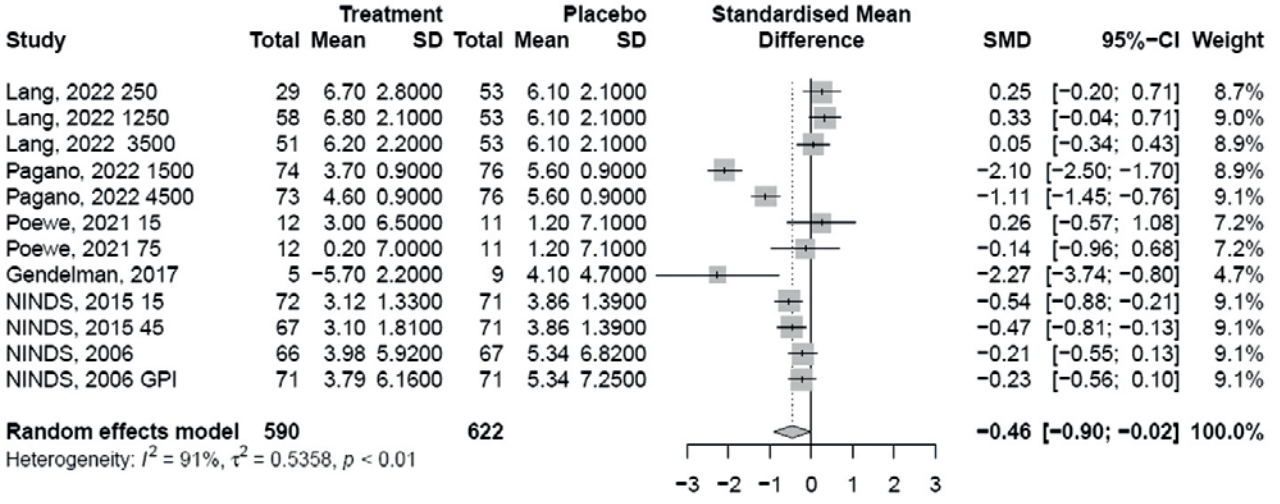
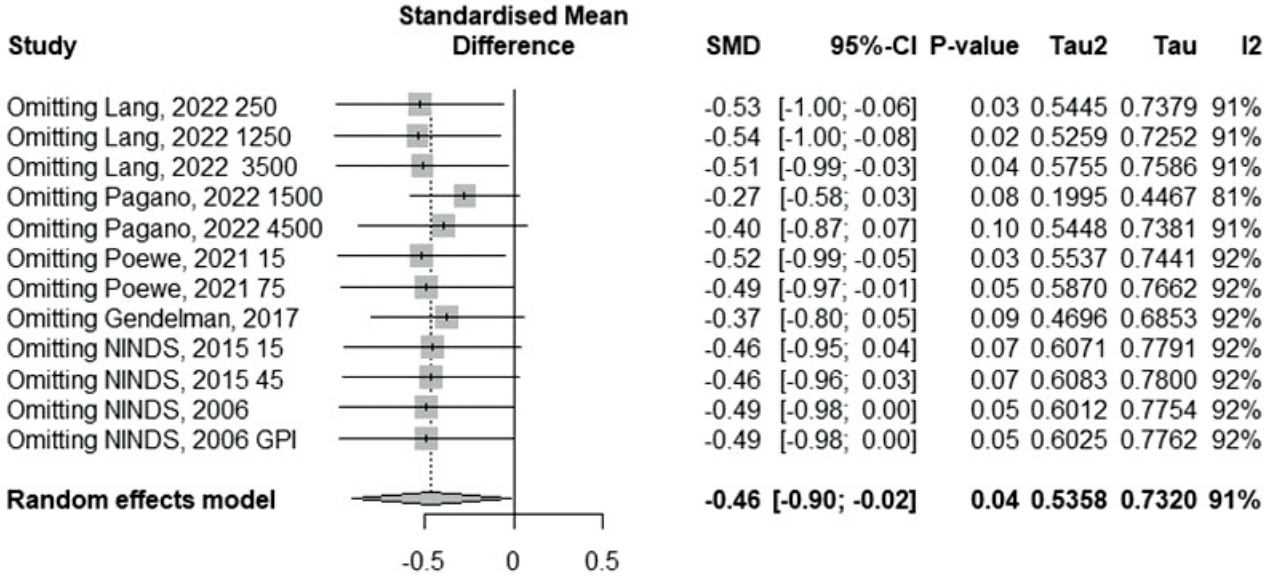


Figure 4. Forest plot of sensitivity analysis.

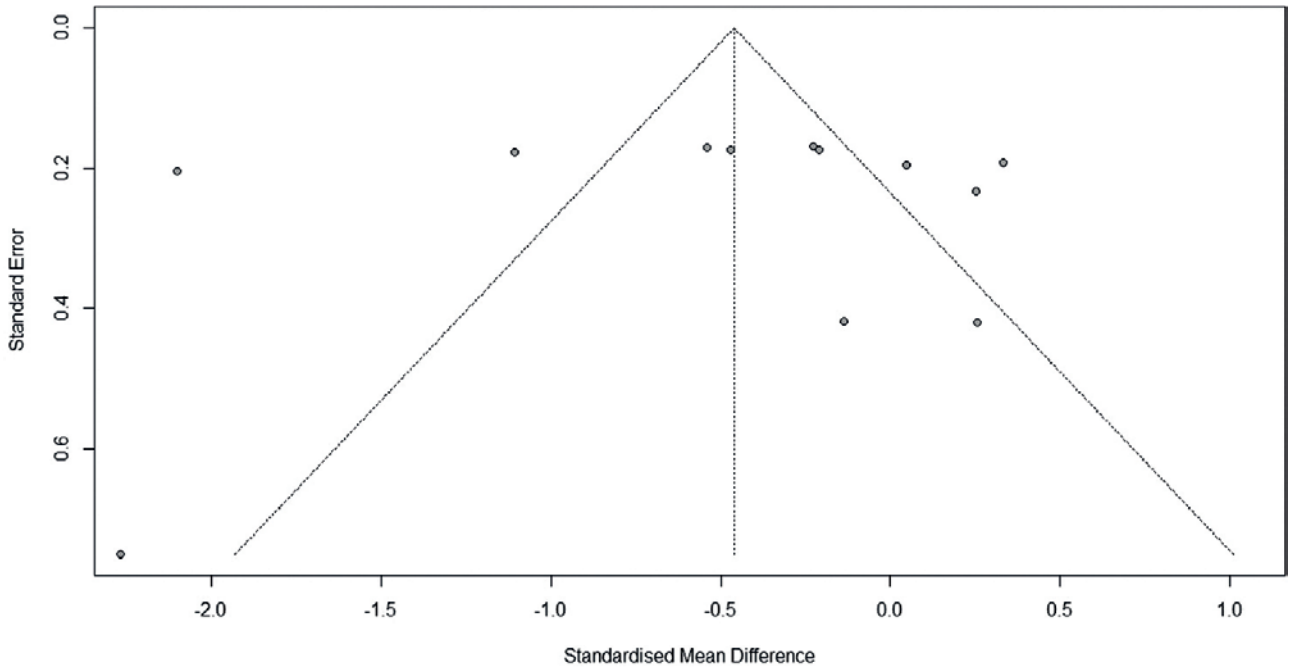


in the change in MDS-UPDR III score between the treatment and placebo groups. However, two studies showed a trend toward separation from the mean (Fig. 3).

Sensitivity was assessed to determine the influence of each study on the overall effect estimate. As shown in Fig. 4, no study had a significant overall effect. The results of the meta-analysis did not change dramatically in magnitude or direction, indicating that the meta-analysis is robust.

Finally, the risk of bias in the meta-analysis was assessed using a funnel plot. Because the plot was too sparsely populated to visually detect asymmetry (Fig. 5), Egger's test was also used. As shown in

Figure 5. Funnel plot.



Supplementary Fig. 2, the plot is symmetrical (intercept = −0.27, P = 0.9337), suggesting no publication bias in the included studies; however, this result should be taken with caution due to the small number of included studies.

Adverse events

Virtually all adverse events reported in the trials were not severe (Table 1). The most common adverse events were related to the route of administration, such as injection site pain, injection site reaction, and infusion reaction. Only the study by Gendelman et al.[20] reported abnormal white blood cell count, elevated creatinine phosphokinase, and pain in the extremities and joints.

DISCUSSION

At present, patients with PD receive only symptomatic treatment. However, new therapeutic approaches such as immunomodulatory drugs and immunotherapies hold promise for improving patients' quality of life and halting disease progression[33]. The neuroinflammatory process that accompanies PD is associated with abnormalities in alpha-synuclein aggregation, chronic glial activation, secretion of proinflammatory cytokines, and the presence of activated immune cells. The relevance of neuroinflammation during PD in brain tissue and cerebrospinal fluid underscores the importance of developing and evaluating drugs to modify this inflammatory profile[34,35]. Immunomodulatory treatments, including those tested with positive results in animal models of PD, have paved the way for therapies being tested in clinical trials.

Seven clinical trials evaluating immunomodulators or immunotherapies were included in this meta-analysis. Although no significant differences were found in the change in MDS-UPDRS III score between the treated group and placebo, even in studies using higher doses (Fig. 2), 2 studies showed a tendency to depart from the mean.

Pagano et al. reported no difference in the change in MDS-UPDRS total score between prasinezumab and a placebo; however, only Part III of the scale was analyzed in this meta-analysis, so it is possible that prasinezumab has little effect on motor improvement. This result may also be due to the fact that the data were not adjusted for multiple comparisons, as acknowledged by the authors[36].

Sargramostim, recombinant human GM-CSF, is the only drug included in this meta-analysis that showed a positive effect on PD. Gendelman et al.[20] reported a significant decrease in the MDS-UPDRS III score (Table 1) in the treatment group at the end of the study (8 weeks) from baseline. A mean change of −5 indicates a significant improvement in motor symptoms. However, this result was not significant when compared to the mean change across studies. This may be due to the small number of patients included in this study (nine on placebo and five on treatment). As shown in the forest plot, the confidence interval (CI) of this study was the largest among the included studies. It is noteworthy that sargramostim increased CD4 + CD25 + CD127lo Treg counts after 2 weeks of treatment, accompanied by an alteration in tryptophan pathway: L-kynurenine and quinolinic acid levels were increased, and serotonin levels decreased. These findings suggest that sargramostim could be an effective immunomodulator; however, trials with a greater sample size and the required power to evaluate clinical outcomes should be conducted. This highlights the need for further research and larger clinical trials in this area.

Cinpanemab (anti-synuclein alpha monoclonal antibody), which had reduced striatal dopamine transporter loss and reversed movement impairment in a mouse model of PD, showed no significant effect compared with the placebo group[37]. PD03A, a short peptide derived from an epitope of the C-terminal region of alpha-synuclein, showed efficacy in inducing antibodies and activating the immune response but had no effect on the MDS-UPDRS III score[24,38]. Pioglitazone, minocycline, and GPI-1485 are drugs currently used in various conditions that have been reported to have neuroprotective effects and evaluated in preclinical models[28,30,39]. Neither pioglitazone, a PPAR-γ agonist; minocycline, a tetracycline used to treat bacterial infections with anti-inflammatory properties that reduce levels of proinflammatory cytokines nor GPI-1485, a neuroimmunophilin ligand with immunosuppressive effects, induced a change in MDS-UPDRS III score and did not improve motor problems in PD patients. It is possible that the lack of significance in the differences is due to (a) the duration of treatments, (b) the sample size, (c) the time of treatment initiation (unlike animal models, we do not know when PD started in patients), and (d) the need for concurrent administration of dopamine or other treatments with the tested drug. As for our meta-analysis study, most of the studies lacked the power to analyze clinical outcomes such as MDS-UPDRS III scores, imaging studies, or immunologic profiles, as well as other cellular tests. It would be beneficial to assess the immune profile of patients by measuring cytokine levels and analyzing T-cell function and phenotypes when evaluating drugs with potential immunologic effects.

Regarding the quality of our meta-analysis, most of the included studies have a low risk of bias in the domains assessed by the Cochrane tool (Supplementary Fig. 1), suggesting a good methodological quality of the included studies. As for the sensitivity test, the omission of any study did not substantially change the magnitude or direction of the result (Fig. 4), so the result of the meta-analysis can be considered robust. With respect to publication bias, although the funnel plot shows some asymmetry in the included studies (Fig. 5), Egger's test (Supplementary Fig. 2) showed no evidence of asymmetry. Thus, it can be assumed that there is no publication bias, although the small number of included studies should also be taken into account.

None of the adverse events were serious and were reported in both the treatment and placebo groups (Table 1). The most common adverse events were related to the route of administration; however, it should be noted that adverse events such as abnormal white blood cell counts or joint pain, which were reported in some of the included trials, could further affect patients who already have a poor quality of life due to PD. Such adverse events may warrant a cost-benefit evaluation of these drugs.

Finally, this study has clear limitations, one of which is the high heterogeneity of the results. This heterogeneity may be the result of methodological differences between the included articles since different drugs were tested and, although they all have immunomodulatory or immunotherapeutic effects, the different molecules were administered by different routes, at different doses and with different treatment durations. In addition, the number of studies found and analyzed was small, and although the total number of patients included in the meta-analysis is adequate, some of the included studies have very small sample sizes. For example, the study by

Gendelman et al.[20] reported a positive effect with a significant mean change in scores; however, because the sample is very small (14 patients), the confidence interval is very wide, making it less meaningful, this is reflected in a lower weight (influence) of the Gendelman's study within the meta-analysis. In addition, it should be noted that most of the included studies were not designed to assess clinical outcomes and clinical improvement, so more information and evaluation are required.

In conclusion, idea of controlling neuroinflammation to halt or delay disease progression or improve symptoms in PD is promising, as shown by pre-clinical studies with positive results; however, no significant effects on motor symptoms were found in the clinical trials included in this review. It is worth noting that in our study, we only assessed motor symptom improvement by MDS-UPDRS III score reports. However, several molecules with immune system activity that is currently being tested were not included because they are in phase 1 and/or have not reported MDS-UPDRS III scores. In addition, we should keep in mind that both the disease and the mechanisms of neuroinflammation are complex, so immunomodulatory therapies are also expected to be intricate and not easy to evaluate. Treatments that target neuroinflammation are valuable not only because they might halt a degenerative disease but also because of the insights they might provide into the relationship between the nervous and immune systems.

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SUPPLEMENTARY DATA

Supplementary data are available at DOI: 10.24875/RIC.24000068. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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