RESEARCH ARTICLE

Safety of Plasma Infusions in Parkinson's Disease

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ABSTRACT: Background: Young plasma infusions have emerged as a potential treatment for neurodegenerative disease, and convalescent plasma therapy has been used safely in the management of viral pandemics. However, the effect of plasma therapy in Parkinson's disease (PD) is unknown.

Objectives: The objective of this study was to determine the safety, tolerability, and feasibility of plasma infusions in people with PD.

Methods: A total of 15 people with clinically established PD, at least 1 cognitive complaint, and on stable therapy received 1 unit of young fresh frozen plasma twice a week for 4 weeks. Assessments and adverse effects were performed/reported on and off therapy at baseline, immediately after, and 4 weeks after the infusions ended. Adverse effects were also assessed during infusions. The primary outcomes were safety, tolerability, and feasibility. Exploratory outcomes included Unified Parkinson's Disease Rating Scale Part III *off* medication, neuropsychological battery, Parkinson's Disease Questionnaire-39, inflammatory markers (tumor necrosis factor-α, interleukin-6), uric acid, and quantitative kinematics.

Results: Adherence rate was 100% with no serious adverse effects. There was evidence of improvement in phonemic fluency ($P = 0.002$) and in the Parkinson's Disease Questionnaire-39 stigma subscore ($P = 0.013$) that were maintained at the delayed evaluation. Elevated baseline tumor necrosis factor-α levels decreased 4 weeks after the infusions ended.

Conclusions: Young fresh frozen plasma was safe, feasible, and well tolerated in people with PD, without serious adverse effects and with preliminary evidence for improvements in phonemic fluency and stigma. The results of this study warrant further therapeutic investigations in PD and provide safety and feasibility data for plasma therapy in people with PD who may be at higher risk for severe complications of COVID-19. © 2020 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: infusions; Parkinson's disease; plasma; young plasma

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Relevant conflicts of interests/financial disclosures: H.M.B.S. serves on a clinical advisory board for Medtronic, Inc.

Received: 24 April 2020; **Revised:** 15 May 2020; **Accepted:** 15 June 2020

Published online 7 July 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28198

Interest in the potential therapeutic role of young plasma infusions for neurodegenerative diseases arose following demonstrations that the infusion of young rodent plasma into older rodents counteracted aging at the molecular, structural, and functional levels in the hippocampus with beneficial effects on cognitive impairment.[1,2] In Alzheimer's disease (AD) animal models, young plasma infusions reduced neuroinflammatory markers,[3] and in humans, platelet rich plasma infusions have an anti-inflammatory effect via reduction of tumor necrosis factor-α (TNF-α) and other neuroinflammatory compounds.[4] These and other preclinical findings were

quickly translated into the clinical setting after it was demonstrated that young fresh frozen plasma (yFFP) infusions in patients with AD were well tolerated without any serious adverse effects.[5]

Parkinson's disease (PD) is characterized by motor and nonmotor symptoms, including cognitive and mood dysfunction.[6] AD and PD have overlapping neuropathological processes,[7] suggesting that treatments that slow neurodegenerative processes in one may also be therapeutic in the other; however, there have been no investigations of the safety, feasibility, or efficacy of yFFP in either animal models of parkinsonism or in human subjects with PD.[2]

Passive immunity after the administration of pathogen-specific antibodies was first developed in 1880 to treat infectious diseases when no vaccines and/or treatment were available.[8] Initially, sources of such antibodies were from the serum of stimulated animals, after which human blood from convalescent patients was also identified as a source.[9] Human convalescent plasma was first identified as a potential therapy during the Spanish flu pandemic of 1918 to 1920, and subsequent meta-analysis revealed reduced mortality risk in the treated patients.[10,11] To date, convalescent plasma therapy has been used safely in the treatment of the severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), and H1N1 viral epidemics, and early reports suggest that this may be a promising intervention in the coronavirus disease 2019 (COVID-19) pandemic.[12-17]

Young and convalescent plasma differ only in the specific antibodies targeted in convalescent plasma; both contain a mixture of inorganic salts, organic compounds, water, and more than 1000 proteins, such as albumin, immunoglobulins, complement, coagulation, and antithrombotic factors. The presence of other proteins such as anti-inflammatory cytokines have been shown to provide immunomodulatory effects, in which elevated levels of proinflammatory cytokines, including TNF-α and interleukin-6, are reduced.[15,18]

Overall, both young and convalescent plasma infusions have been well tolerated in healthy adults, although adverse events (AEs), such as skin and allergic reactions, have been routinely documented.[5,19] Antibody-dependent enhancement resulting in an increase in the intensity of infection may occur with the use of convalescent plasma, in which antibodies that are supposed to protect the host actually facilitate viral entry and replication in the target cell.[20] The possibility of antibody-dependent enhancement is a concern in the development of immunotherapies and vaccines and potentially as an unforeseen AE from young plasma infusions. People with PD may be at a higher risk of severe complications of coronavirus disease 2019 (COVID-19) and for adverse effects of plasma therapies as a result of older age, susceptibility to pneumonia, concomitant physical morbidity, and evidence of underlying neuroinflammation that has led to autoimmune mechanisms of disease pathogenesis.[21-23]

The goal of the present study was to establish the safety, feasibility, and tolerability of yFFP intravenously administered to people with moderate-stage PD in an open-label, phase I clinical trial. Exploratory outcomes aimed to establish the effect of yFFP infusions on the domains of motor function, cognition, mood, quality of life (QOL), and inflammatory blood markers. The results of this study are important not only in the potential development of plasma therapy for PD but also for people with PD who might be candidates for convalescent plasma therapy during the COVID-19 pandemic.

Methods

Human Subjects and Enrollment Criteria

Target enrollment for the study was 15 patients with idiopathic PD. Inclusion criteria included a diagnosis of clinically established PD for at least 2 years with a ≥ 30% improvement in the Movement Disorder Society (MDS)–Unified Parkinson's Disease Rating Scale (UPDRS III, motor) score *on* compared with *off* therapy, age of 50 to 80 years, on stable therapy (dopaminergic medication and/or deep brain stimulation parameters) for at least 4 weeks prior to screening and throughout the duration of the study, at least 1 cognitive complaint with a Montreal Cognitive Assessment[24] (MoCA) score between 23 and 28, and a stated willingness to comply with the trial protocol.

Exclusion criteria included a medical history of gout, congestive heart failure, renal failure, uncontrolled atrial fibrillation, stroke, anaphylaxis, blood coagulation disorder, or immunoglobulin A deficiency; participation in any other interventional clinical trial; the inability to travel to Stanford for baseline, outcome, or infusion visits; a nonambulatory state (Hoehn and Yahr stage V[25]) in the *off* or *on* therapy state; clinically determined dementia; clinical suspicion or diagnosis of atypical forms of parkinsonism or essential tremor; pregnancy or an unwillingness to use an adequate birth control method for the duration of and 6 months beyond study participation; positive test results for hepatitis B, hepatitis C, or HIV at screening; treatment with any human blood product (including intravenous immunoglobulin) during the 6 months prior to screening or during the trial; concurrent daily treatment with benzodiazepines, typical or atypical antipsychotics, long-acting opioids, or other medications that in the investigator's opinion would interfere with cognition; or any other condition or situation that the investigator believed may interfere with the safety of the patient or the intent and conduct of the study.

The study was approved by the Stanford University Institutional Review Board and registered as NCT02968433 at ClinicalTrials.gov. All participants consented by completing an Institutional Review Board–approved written informed consent form prior to completing any study-related testing.

Trial Design

The trial required patients to attend 14 research visits: 2 baseline screening neurological visits (*on* and *off* therapy), 8 infusion visits (twice a week for 4 weeks), 2 neurological visits immediately following the last infusion (*on* and *off* therapy), and 2 neurological visits 1 month after the last infusion (*on* and *off* therapy). The neurological visits at baseline, immediately following the last infusion, and 1 month after the last infusion included a neuropsychological evaluation while the patient was on therapy.

The initial infusion visit was scheduled within 2 weeks of the baseline neuropsychological and lab testing. One unit (approximately 250 mL) of young plasma was administered per visit, twice a week for 4 consecutive weeks (8 infusion visits). The patients' last infusion was always completed in the morning so that the *on* therapy immediate outcome testing was completed on the same day; the *off* therapy immediate outcome visit was performed the following morning. The same comprehensive testing, both *on* and *off* therapy, was repeated over 2 days, 4 weeks after the last plasma infusion. Details of the infusion protocol can be found in Supplementary Information.

Baseline and Outcome Testing

At baseline, all patients were tested in their best *on* therapy state and again the following day in the practically defined *off* state. Long-acting dopaminergic medications were withdrawn over 24 hours and short-acting medications were withdrawn over 12 hours prior to *off* therapy visits. For those on deep brain stimulation, stimulation was turned OFF at least 15 minutes before any experiments took place.[26] Baseline, immediate postinfusion, and delayed postinfusion assessments included the Movement Disorder Society–UPDRS III *on* and *off* therapy, the UPDRS IV (complications of therapy scale), *on* therapy cognitive testing,[27] and a repetitive wrist flexion extension (rWFE) task, detailed in the Supplementary Information. The *off* therapy UPDRS III was additionally scored using shuffled video records by another certified rater who was blinded to the study visit.

Neuropsychological visits occurred the same day as the neurological *on* therapy visits, immediately following the last infusion, and again *one* month after the last infusion. The battery was administered by a neuropsychologist and is detailed in the Supplementary Information. QOL changes were tracked using the self-report Parkinson's Disease Questionnaire–39 (PDQ-39).[7] Blood levels of TNF-α, interleukin-6, and uric acid were also drawn at baseline and outcome visits.

Data Collection and Analysis

All data was entered in REDCap,[28] a secure, Health Insurance Portability and Accountability Act (HIPPA)–compliant database that was accessible by research staff only. AEs were recorded through REDCap and categorized using the Common Terminology Criteria for Adverse Events (version 4.0). Adherence rate was calculated for each patient and defined as the quotient of the total number of study visits attended divided by the total number of scheduled study visits. AEs were reviewed by 1 or both movement disorders neurologists (H.M.B.S., M.L.) and the transfusion medicine specialist (N.S.), and subsequently categorized based on the likelihood that a discrete event was related to the study intervention (probably, possibly, or not related).

Raw scores and normative scores were calculated for all cognitive, mood, and QOL measures according to standardized procedures across all 3 time points. Exploratory outcomes were conducted to determine change from baseline for the measures reported previously.

Statistics

All analyses were performed using R 3.5.0.[29] Linear mixed effects models with a random intercept for patient were used to model the effect of visit on outcomes of interest. These models are robust to missing observations under mild missingness assumptions, such as missing completely at random, and allow for the inclusion of participants who are missing data from 1 or 2 observation periods. Missingness was not especially prevalent in these data, and where present, it was attributed to an arguably missing completely at random process (lost or corrupted video data). Visit was modeled categorically and its statistical significance was assessed via the Satterthwaite *F* test. This test produces a single *P* value for visit for each model. In addition, each model was used to estimate mean outcomes at each visit as well as differences between outcomes from visit to visit. Given the exploratory nature of these analyses, no adjustments for multiple testing were made.

Results

From 54 people with PD who were phone screened, 21 provided written consent to participate in the study. After consent but prior to establishing study visits, 2 patients were exited: 1 was unwilling to be tested *off* therapy and 1 was unwilling to commit to the study visit schedule. At baseline, 3 patients failed to meet screening criteria and were exited from the study before

treatment began: 2 patients had MoCA scores above the inclusion range, and 1 patient did not satisfy the Movement Disorder Society clinical diagnostic criteria for PD.[30]

Table 1 details the demographic data of the 15 patients (5 women) who completed the study. The PD cohort was representative of moderate-stage PD with a mean ± standard deviation age of 63 ± 8.30 years and disease duration of 7.93 ± 3.51 years, and with 16.87 ± 2.42 years of education. At baseline, all patients exhibited a good response to dopaminergic medication (mean UPDRS III *off* and *on* medication scores were 34.67 ± 15.05 and 18.13 ± 11.99, respectively), did not have dementia, and had a mean baseline MoCA score of 26.60 ± 1.59.

Primary Outcomes

yFFP infusions were safe and well tolerated. No serious AEs were reported throughout the course of the study; however, several mild AEs occurred. AEs included transient skin reactions; involuntary movements; and musculoskeletal, central nervous system, or systemic symptoms (Table 2). Infusions did not cause volume-related AEs or abnormal lab values. Comprehensive blood tests, including complete blood count, chemistries, and liver and kidney function tests, were not adversely affected by the plasma infusions.

Among the 16 patients for whom study visits were set up, 53 minor AEs were reported, of which 14 (26.42%) were categorized as probably related (Table 2). Three (5.66%) AEs were possibly related, and 36 (67.92%) were categorized as not related. Mean adherence rate was 95.83% for the 16 patients and 100% after accounting for the 1 patient's decision to withdraw early from the study after experiencing a macular rash more than 24 hours after the second infusion. The rash was not observed by study personnel as

TABLE 2. Categorization of AEs based on the likelihood of relatedness to intervention

AE	No. (%)
Probably related AE	
Bruising	1 (1.89)
Skin and subcutaneous tissue disorder	13 (24.53)
Possibly related AE (by category)	
Cough	2 (3.77)
Hypotension	1 (1.89)
Unrelated AE	
Nervous system disturbance	4 (7.55)
Bloating	1 (1.89)
Urinary frequency disturbance	2 (3.77)
Stomach pain	1 (1.89)
Back pain	1 (1.89)
Involuntary movements	8 (15.09)
Musculoskeletal and connective tissue disorder	4 (7.55)
Chest tightness	1 (1.89)
Sore throat	1 (1.89)
Fall	1 (1.89)
Flu-like symptoms	2 (3.77)
Tremor	1 (1.89)
Generalized muscle weakness	1 (1.89)
Sleep decrease	2 (3.77)
Headache	2 (3.77)
Skin and subcutaneous tissue disorder	2 (3.77)
Gastrointestinal	1 (1.89)
Pain in extremity	1 (1.89)

No. (%) = number of AEs in a specific category and percentage of the total AEs in that category. Table includes data for patients who received at least 1 infusion.
AEs, adverse events.

TABLE 1. Demographic data for each patient

	Patient Demographics					
Patient	Age, y	Disease Duration, y	MoCA Score	Baseline UPDRS III *Off* Therapy	Baseline UPDRS III *On* Therapy	Hoehn and Yahr (*Off* Therapy)
1	71	9	28	28	13	2
2	71	7	26	27	15	2
3	51	7	28	38	22	2
4	64	8	27	51	15	3
5	56	9	24	39	16	2
6	55	13	25	54	38	2
7	70	5	27	26	15	3
8	58	7	28	28	12	2
9	51	6	28	51	17	2
10	74	4	27	56	47	2
11	69	14	28	46	31	2
12	55	9	26	11	7	2
13	66	14	23	37	14	3
14	74	4	28	16	8	2
15	60	3	26	12	2	2
M (SD)	63 (8.30)	7.93 (3.51)	26.60 (1.59)	34.67 (15.05)	18.13 (11.99)	2.20 (0.41)

MoCA, Montreal Cognitive Assessment; UPDRS III, Unified Parkinson's Disease Rating Scale Part III; M, mean; SD, standard deviation.

it had resolved by the time the patient was evaluated. The patient also admitted to eating unusual food that day and did not experience any skin reaction during either of the 2 infusions.

Exploratory Outcomes

There was immediate and maintained improvement in phonemic fluency and in 1 PDQ-39 subscore (stigma: self-perceived negative attributes; Table 3). There was no significant change in any other cognitive or QOL scores. There was immediate and maintained improvement in the *off* therapy unblinded total UPDRS III scores and in both the more and lesser affected unblinded lateralized scores (Table 3); however, there was no significant change detected in the *off* therapy blinded rater video assessment of the UPDRS III scores. The trend was toward improvement with a 2.04 decrease in median blinded UPDRS III (excluding rigidity) scores at the 4-week postinfusion visit; the clinically important difference for the total UPDRS III is 2.3 to 2.7.[31] Patients did not experience any plasma-related complications of therapy, as measured by the UPDRS IV, and did not experience additional freezing-of-gait disturbances related to the study intervention, as measured by the FOG-Q (Table 3).

Baseline Elevated Inflammatory Markers Were Lower 4 Weeks After Plasma Infusions

Exploratory observation revealed that 8 of 15 (53.33%) patients had elevated plasma TNF-α levels at baseline (TNF-α > 22), which decreased in all 8 patients

Table 3. Exploratory outcomes (means and 95% confidence intervals) for all neuropsychological, mood, quality-of-life, and motor tests/questionnaires

Test	Baseline	Immediate	Delayed	P
Neuropsychological/cognitive tests				
Wechsler Abbreviated Scale of Intelligence–II				
Block construction	34.73 (27.45–42.02)	35.60 (28.32–42.88)	37.47 (30.18–44.75)	1
Matrix reasoning	17.47 (14.87–20.06)	17.27 (14.67–19.86)	20.13 (17.54–22.73)	1
Symbol Digit Modalities Test				
Written	44.80 (39.14–50.46)	47.07 (41.40–52.73)	49.40 (43.74–55.06)	0.090
Oral	53.67 (46.89–60.44)	57.40 (50.62–64.18)	57.73 (50.96–64.51)	0.323
Trail Making Test				
Part A	32.53 (27.63–37.44)	29.27 (24.36–34.17)	29.07 (24.16–33.97)	1
Part B	83.20 (62.64–103.76)	72.87 (52.31–93.42)	73.53 (52.98–94.09)	1
Verbal fluency				
Phonemic (COWAT; Letters-FAS)	41.13 (34.75–47.52)	44.73 (38.35–51.12)	48.07 (41.68–54.45)	**0.002**
Semantic (Animal Naming)	21.40 (19.17–23.63)	22.40 (20.17–24.63)	23.07 (20.84–25.29)	1
CogState (GML)	71.47 (53.15–89.79)	54.87 (36.55–73.19)	60.53 (42.21–78.85)	1
Mood				
Beck Anxiety Inventory	10.66 (6.06–15.25)	7.60 (3.05–12.15)	8.47 (3.92–13.02)	1
Beck Depression Inventory	9.92 (5.69–14.15)	8.13 (3.93–12.34)	8.07 (3.86–12.27)	1
Quality of life				
PDQ-39 (total score)	71.81 (59.51–84.10)	66.73 (54.49–78.98)	64.40 (52.16–76.64)	0.253
Mobility	17.33 (13.38–21.28)	16.47 (12.53–20.41)	15.80 (11.86–19.74)	1
Activities of daily living	12.05 (10.29–13.82)	11.60 (9.85–13.35)	10.53 (8.79–12.28)	0.286
Emotional well-being	10.60 (7.75–13.45)	10.13 (7.30–12.97)	10.00 (7.16–12.84)	1
Stigma	7.42 (6.22–8.63)	6.20 (5.01–7.39)	5.53 (4.34–6.72)	**0.013**
Social support	5.57 (3.99–7.16)	5.00 (3.43–6.57)	5.33 (3.76–6.90)	1
Cognition	6.90 (5.53–8.28)	6.87 (5.50–8.23)	6.80 (5.43–8.17)	1
Communication	5.33 (4.31–6.36)	5.20 (4.19–6.21)	4.60 (3.59–5.61)	1
Bodily discomfort	6.53 (5.25–7.82)	5.27 (4.00–6.53)	5.80 (4.53–7.07)	0.734
Motor				
Unblinded UPDRS III score	34.67 (27.95–41.38)	26.13 (19.42, 32.85)	25.20 (18.48, 31.92)	< 0.001
More affected	15.27 (12.29–18.24)	11.47 (8.49–14.44)	11.73 (8.76–14.71)	< 0.001
Less affected	9.33 (6.95–11.72)	7.47 (5.08–9.85)	6.60 (4.22–8.98)	0.007
Blinded UPDRS III score (excluding rigidity)	21.43 (15.84–27.01)	19.77 (14.13–25.42)	19.39 (13.74–25.03)	0.483
More affected	9.21 (6.72–11.71)	7.59 (5.06–10.12)	7.66 (5.14–10.19)	0.141
Less affected	4.64 (3.07–6.21)	4.55 (2.95–6.15)	4.84 (3.24–6.44)	0.907
Freezing of Gait Questionnaire	4.57 (2.58–6.56)	4.57 (2.58–6.56)	4.50 (2.51–6.49)	0.995
UPDRS IV	4.77 (3.11–6.43)	3.81 (2.09–5.54)	4.67 (2.98–6.35)	0.188

Significant *P* values are indicated in bold.
CogState, computerized cognitive tests; COWAT, Controlled Oral Word Association Test; FAS, F-A-S mesaure of phonemic fluency; GML, Groton Maze Learning; PDQ-39, Parkinson's Disease Questionnaire–39; UPDRS III, Unified Parkinson's Disease Rating Scale Part III; UPDRS IV, Unified Parkinson's Disease Rating Scale Part IV.

TABLE 4. All patients' baseline TNF-α levels; types of skin reaction experienced, if any; and TNF-α levels 4 weeks postinfusion

Patient	Skin AE	TNF-α (pg/mL)	
		Baseline	Four weeks post
1	None	59	21
2	None	< 5	3.4
3	Itching and hives, 3 different limbs	173	2.5
4	Itchiness, 2 hives	107	71
5	Urticaria, welts, bumps behind ear, redness of face	24	2.4
6	None	16	2.4
7	None	50	4.6
8	Itchiness behind left ear, chest and back; hives; swelling of inner left eye duct and eyelid	946	2.7
9	Welts on temple and left arm, rash acneiform, small red blotches on back	96	30
10	Swollen right inner arm	195	20
11	None	< 5	< 5
12	None	< 5	< 5
13	None	< 5	< 5
14	Welt on left side of chest	5	< 5
15	None	< 5	< 5

Abnormal values are indicated in bold text. Normal range is ≤22 pg/mL.
TNF-α, tumor necrosis factor-α; AE, adverse event.

at the delayed (4 weeks postinfusion) evaluation (Table 4). Table 4 demonstrates that 6 of the 8 patients who had elevated baseline TNF-α levels reported 1 or more skin reactions during infusions. Only 1 patient with a normal baseline TNF-α reported a skin reaction.

Baseline interleukin-6 levels were normal in 13 of 15 patients and remained normal after the infusions, and baseline uric acid levels were normal in all but 1 of the patients (Supplementary Information Table S1).

Quantitative Kinematics

A total of 12 patients completed the rWFE task at baseline and at both outcome visits. In the patients who completed the task at all 3 time points, there was no significant change in the mean angular velocity, the variability of mean angular velocity, or the regularity of the interstrike interval in the more or lesser affected hands (Table 5).

Discussion

This is the first study demonstrating that 4 weeks of twice-weekly infusions of 1 unit of yFFP in people with clinically established PD was safe, feasible, and well tolerated with no serious AEs. One patient voluntarily withdrew after experiencing a transient macular rash over 24 hours after receiving the second infusion, which was categorized as unrelated, and the adherence rate was 100% in the remaining 15 patients. The most common adverse effects were mild skin reactions during infusions, which are common during clinical plasma infusions but still may be a source of discomfort for people with PD.[32]

Preliminary Evidence of the Therapeutic Effect of Young Plasma Infusions for PD

Analysis of cognitive and QOL exploratory outcomes revealed significant improvements in phonemic fluency and in the stigma subscore of the PDQ-39. Improvements in both phonemic fluency and in the stigma subscore were evident immediately after the infusions and did not deteriorate after a 4-week washout of the infusions. The degree of cognitive impairment in this study was mild overall. Although not at ceiling, the group mean score for each cognitive measure fell within the normal range. There were 3 patients with MoCA scores lower than 26, which is the suggested cut-off for cognitive impairment in PD, and 3 patients had a baseline MoCA score of 26. Four patients met criteria for mild cognitive impairment (MCI) level 1[33] when taking into consideration the complete test battery. Specifically, on the phonemic verbal fluency task, only 4 patients had scores below the normal range (ie, 1 standard deviation below the mean) based on demographic normative data.

Verbal fluency tests both verbal ability and executive control and is one of the most common early-stage cognitive deficits in PD; impaired phonemic fluency has been correlated with smaller caudate volumes in early-stage PD.[34-38] There was no control group in this phase I study, but the baseline phonemic fluency scores in this cohort were similar to those from a different cohort of 36 patients with PD (of similar age and education) whose phonemic fluency scores were significantly lower than 52 age-matched controls (Table 3).[35] Although it has been determined that the practice effect for repeated cognitive testing is small among patients with PD,[39] this

TABLE 5. rWFE quantitative bradykinesia outcomes (means and 95% confidence intervals) for Vrms, CV Vrms, and the regularity of the ISI or CV ISI on the MA and LA

Metric	Baseline	Immediate	Delayed	P
MA Vrms (deg/sec)	305.13 (196.72–413.54)	339.66 (231.24–448.07)	312.39 (203.98–420.81)	0.60
MA CV Vrms	0.29 (0.20–0.38)	0.19 (0.10–0.29)	0.26 (0.17–0.35)	0.87
MA CV ISI	0.16 (0.07–0.26)	0.11 (0.01–0.20)	0.17 (0.08–0.27)	0.94
LA Vrms	414.47 (295.08–533.86)	411.26 (291.87–530.65)	403.00 (283.61–522.39)	1
LA CV Vrms	0.16 (0.09–0.22)	0.17 (0.12–0.24)	0.18 (0.11–0.24)	1
LA CV ISI	0.09 (0.05–0.14)	0.09 (0.04–0.13)	0.10 (0.05–0.15)	1

rWFE, repetitive wrist flexion extension; Vrms, mean angular velocity; CV Vrms, variability of mean angular velocity; ISI, interstrike interval; CV ISI, rhythmicity; MA, more affected; LA, less affected.

same study determined that a reliable change index in phonemic fluency would be of the order of an increase of 11.09 or a decrease of 12.69 in the phonemic fluency correct score. In the current study, the median improvement was below this, and only 3 of 15 patients showed an improvement that would be considered reliable. As such, although the improvement in this study was significant, it should be regarded as preliminary.

In designing this first of its kind study in PD, we targeted people with moderate-stage PD and mild cognitive deficits (MoCA 23–28) rather than focusing on those with dementia. Dementia is usually encountered in later stages of idiopathic PD,[40] and as it has been proposed from animal literature that any effect of young plasma therapy may be restorative in nature,[1,2,41] we hypothesized that yFFP infusions would be more likely to demonstrate a difference in early to moderate stages of neurodegeneration, when the cell loss and pathological burden was not extreme. Phonemic fluency may be such a task that is impaired in earlier stages of PD and possibly sensitive to such interventions.

The experience of stigma by people with PD reflects their perceived negative image in and reception by society that may lead to shame, embarrassment, and withdrawal from public spaces.[42] Experienced stigma has been shown to be a key determinant of overall QOL in PD and has been shown to have a higher correlation with QOL than with depression or motor difficulties of daily living.[43] The maintained improvement of stigma after yFFP infusions may make a meaningful difference in QOL for patients with PD. This result should be interpreted as preliminary because of the potential of a placebo effect of a phase I study but suggests that the inclusion of stigma and other QOL scores will be important in larger placebo-controlled studies of the efficacy of yFFP for PD.

Analysis of the blinded UPDRS III scores revealed no significant improvement after yFFP infusions, although there was a downward trend of the median UPDRS III scores (Table 3); the difference in the mean UPDRS III from baseline to the 4 weeks postinfusions was 2.04, slightly below the clinically important difference for the UPDRS III of 2.3 to 2.7[31]; however, the blinded scores did not include rigidity, so the clinically important difference may be lower. These analyses omitted 1 patient whose baseline video was missing and only gave 1 statistical outcome despite 2 outcome time points. The unblinded UPDRS III scores demonstrated significant improvement both immediately and 5 weeks postinfusions; however, during analysis, it was determined that the largest discrepancy between the blinded rater's scores and those of the unblinded data set were in the baseline scores. As such, we believe that the unblinded UPDRS III scores are interesting but less reliable.

Reduction in Peripheral Inflammatory Markers After Young Plasma Infusions

Exploratory observations demonstrated that 8 of 15 patients had an elevated peripheral TNF-α level at baseline, which was lower 4 weeks after the end of the yFFP infusions in all 8 patients; there was no elevation of the normal baseline TNF-α levels in the other 7 patients postinfusion. Of the 8 patients with elevated baseline TNF-α levels, 6 experienced 1 or more skin reactions during infusions. It is unclear whether the elevated TNF-α status directly contributed to skin reactivity, but it was interesting that only 1 of 7 patients with normal baseline TNF-α had a skin reaction, which did not occur until the seventh infusion. Skin reactions occurred in a larger percentage of the present PD cohort than was seen in the AD cohort.[5]

TNF-α is a proinflammatory cytokine that has been shown to be elevated in the postmortem brains of people with PD and in animal models of parkinsonism.[44-49] McCoy and colleagues[50] demonstrated that soluble TNF signaling was responsible for nigral dopaminergic neuron loss in the 6-hydroxydopamine (6-OHDA) rodent parkinsonian model, either by neuroinflammatory mechanisms or oxidative toxins. Inhibition of soluble TNF reduced neuroinflammation and dopaminergic neuron loss, suggesting it may be a molecular source of disease progression and a potential point of intervention for disease-modifying therapies. Whether reducing peripheral TNF-α translated to a

reduction in central TNF concentrations remains to be demonstrated, but this preliminary data suggest a potential anti-inflammatory role for yFFP therapy in PD and would support the use of plasma therapy in patients with PD with severe COVID-19 infection and evidence of an elevated immune response. This study was not powered to compare the improvement in inflammatory markers with motor or cognitive improvement, making this an important area for further investigation.

Limitations

As there are no preclinical investigations of young plasma infusions in parkinsonian animal models and this initial trial was a phase I feasibility study, these exploratory outcomes should be taken as preliminary given the possible placebo effect. The cohort was small, and all results including safety are nongeneralizable; the study's statistical model did not adjust for multiple testing, and no statistical analysis was performed on the exploratory analysis of the blood markers as the study was not powered for this and values were reported as ranges rather than absolute values.

Conclusions

Four weeks of twice-weekly yFFP infusions were safe, feasible, and well tolerated in moderate-stage PD with no serious AEs and a 100% adherence rate in 15 people. Exploratory outcome measures indicated significant immediate and maintained improvements in phonemic fluency and in the stigma subscore of the PDQ-39. A majority of patients had elevated markers of peripheral inflammation at baseline that were decreased 4 weeks postinfusion, indicated via a reduction in peripheral TNF-α. Although the unblinded UPDRS III scores improved, they did not remain significant after the blinded UPDRS III scores were calculated. The results of this study demonstrate that yFFP was safe in a small cohort with PD and with potential therapeutic effects, warranting further investigation into the potential anti-neuroinflammatory mechanism of plasma in larger, multicenter, double-blinded clinical trials. These results also support the safety of cautious use of plasma therapy in patients with PD with severe COVID-19 infection. ●

Acknowledgments: The authors wish to thank Johanna O'Day for assistance with data collection; Jordan Seliger, Christine Lin, Bharati Sanjanwala, Kara Richardson, and Emma Adair for assistance with the comprehensive database audit, database management, and patient recruitment; and Brent Bluett for assistance with data interpretation.

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Supporting Data

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