RESEARCH ARTICLE

Human Fetal Cell Therapy in Huntington's Disease: A Randomized, Multicenter, Phase II Trial

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ABSTRACT: Background: Huntington's disease is a rare, severe, inherited neurodegenerative disease in which we assessed the safety and efficacy of grafting human fetal ganglionic eminence intrastriatally.
Methods: Patients at the early stage of the disease were enrolled in the Multicentric Intracerebral Grafting in Huntington's Disease trial, a delayed-start phase II randomized study. After a run-in period of 12 months, patients were randomized at month 12 to either the treatment group (transplanted at month 13–month 14) or the control group and secondarily treated 20 months later (month 33–month 34). The primary outcome was total motor score compared between both groups 20 months postrandomization (month 32). Secondary outcomes included clinical, imaging, and electrophysiological findings and a comparison of pregraft and postgraft total motor score slopes during the entire study period (month 0–month 52) regardless of the time of transplant.
Results: Of 54 randomized patients, 45 were transplanted; 26 immediately (treatment) and 19 delayed (control). Mean total motor score at month 32 did not differ between groups (treated controls difference in means adjusted for M12: +2.9 [95% confidence interval, −2.8 to 8.6]; $P = 0.31$). Its rate of decline after transplantation was similar to that before transplantation. A total of 27 severe adverse events were recorded in the randomized patients, 10 of which were related to the transplant procedure. Improvement of procedures during the trial significantly decreased the frequency of surgical events.We found antihuman leucocytes antigen antibodies in 40% of the patients.
Conclusion: No clinical benefit was found in this trial. This may have been related to graft rejection. Ectopia and high track number negatively influence the graft outcome. Procedural adjustments substantially improved surgical safety. (ClinicalTrials.gov NCT00190450.)

Key Words: cell therapy; Huntington's disease; MIG-HD; phase 2 trial

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Members of the Multicentric Intracerebral Grafting in Huntington's Disease Group are listed in the Appendix.

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Huntington's disease (HD) is a rare inherited neurodegenerative disorder that causes cognitive, behavioral, and motor deficits, often beginning in early adulthood. Genetic diagnosis is unequivocal for patients with more than 39 CAG repeats in the huntingtin gene.[1] Despite intense pathophysiological research, disease-modifying treatments remain elusive, and patients have a mean survival, with considerable dispersion, of 20 years after motor onset.[2] Gene-silencing therapies are promising but will probably be more effective for prevention than restoration. Multiple therapeutic strategies would presumably be required, particularly for individuals already displaying striatal degeneration.

In HD, degeneration of neurons is particularly marked in the striatum, although not exclusive to this region.[3] Striatal quinolinic acid lesions in experimental animals indicate that massive losses of striatal medium-sized spiny neurons, as occur in HD, can trigger progressive cortical projection neuron degeneration. Homotopic transplantation of cells derived from the ganglionic eminence (the fetal zone giving rise to the striatum) can replace the lost striatal neurons in rodent and nonhuman primate quinolinic acid lesion models, partially restoring frontostriatal connections and striatal efferent links to output nuclei and promoting recovery of cognitive and motor functions.[4,5] Despite little neurodegeneration in R6/2 transgenic mice,[6] modest improvement in locomotion was recorded after ganglionic eminence grafting.[7] Functional improvement was also reported in transgenic models following stem cell–derived transplants (eg, references 8,9). Since the 1990s, 70 patients with HD[10] have been enrolled in open-label, nonrandomized, single-center trials (1–16 participants) of striatum-reconstructing treatments. These studies were too heterogeneous (different cell sources, tissue preparations, and surgical protocols) and underpowered to be conclusive or to drive improvements for future trials. Nevertheless, some patients showed clear signs of sustained improvement.[11-13] A graft–host connection was demonstrated in postmortem samples,[14] with structures resembling normal striatum in the grafted region, cortical and nigral afferents from the host, and efferent to downstream pallidal nuclei and substantia nigra.[15,16] International guidelines consider cell transplantation into the brain to be safe[17,18] despite some reports of overgrowth, graft tissues ectopic to the target area,[19,20] and subdural hematomas (SDHs).[14]

We set up a phase II, randomized controlled trial, Multicentric Intracerebral Grafting in Huntington's Disease (MIG-HD), to assess the safety and efficacy of human fetal cell intrastriatal transplantation in patients with early-stage HD. This report summarizes the main study findings and key lessons learned during the course of the trial. We identified factors that may influence transplant functionality for consideration in future trials.

Methods

Study Design and Oversight

MIG-HD was a multicenter, randomized, phase II study assessing the safety of intrastriatal human fetal cell transplantation and its effect on motor function in patients with early-stage HD. The study was conceived as a delayed-start design, where active treatment is sequentially provided to all participants over time so that all patients could eventually benefit from the transplantation procedure.[21] The study was approved by the institutional review boards of Henri Mondor Hospital in France and Erasme Hospital in Belgium. It complied with the Helsinki Declaration, current Good Clinical Practice guidelines, and local laws and regulations. Written informed consent was obtained from patients at month 0 (M0) or month 1 (M1).[22] An independent safety committee monitored the study conduct, the collected data, and any severe adverse events (SAEs). The protocol was registered at ClinicalTrials.gov (NCT00190450). Methodological details are provided in the Supplementary Methods.

Participants

Consenting patients with genetic diagnoses of HD underwent transplantation at 6 French and Belgian hospitals between 2001 and 2010; their follow-up to month 52 (M52) was completed in 2013. The main inclusion criteria were having manifest HD for ≥1 year, >36 CAG repeats in the huntingtin gene, aged 18 to 65 years, total motor score (TMS) >5 on the Unified Huntington's Disease Rating Scale (UHDRS), and total functional capacity score > 9. The main exclusion criteria were Mattis Dementia Rating Scale score < 120 and contraindication for surgery or magnetic resonance imaging (MRI) (Supplementary Methods).

Randomization and Masking

After a 1-year run-in period designed to verify patients' compliance and exclude unusual patterns of clinical deterioration, the patients were randomly assigned at month 12 (M12) in a 1:1 ratio either to treatment (receiving transplant at month 13–month 14) or to the (initially untreated) control group, which were subsequently grafted 20-months later (month 33–month 34) (Fig. S1). Randomization was computer generated, with centralized allocation concealment. A randomization list prepared at the Henri Mondor Clinical Research Unit with Nquery software (Statistical Solutions Ltd., Boston, MA) was used. Participants and investigators responsible for clinical follow-up were not blind to treatment allocation. However, the validity of the primary outcome (UHDRS TMS excluding rigidity) was assessed by video recordings at M12, month 32 (M32), and M52 and scored by specialists not involved in patient follow-up and recruitment and blind to treatment allocation (Fig. S2).

Procedures

Small blocks of whole ganglionic eminences from 1 to 3 8.5-week-old to 12-week-old fetuses (mean ± standard deviation, 1.6 ± 0.6) per grafting session were implanted stereotactically, within 48 hours of retrieval, into the striatum ipsilateral to the dominant hand. A mean of 2.45 ± 3.03 months later, the contralateral striatum was grafted (Supplementary Methods). Cells were injected

through 6 tracks (mean 4.91 ± 1.46; range 3–6) within the head of the caudate nucleus (precommissural and commissural) and the putamen (1 in each of precommissural and commissural and 2 in post-commissural putamen). This totaled a volume of 206.0 ± 43.1 μL unilaterally, distributed as 8 deposits per track (mean 5.1 ± 1.0 μL by deposit) with significant variations across centers. Two tracks were omitted after the first 29 grafting sessions to avoid SDH in patients with major striatal atrophy. Cerebrospinal fluid leakage was limited by confinement to bed and hyperhydration for 48 hours after surgery.

Immunosuppression was achieved with cyclosporine A, beginning 3 days before surgery (400 mg/day, then adjusted to maintain blood concentrations between 100 and 150 mg/L), prednisolone (0.25 mg/kg per day), and azathioprine (0.75 mg/kg per day) both initiated on the day of surgery. Cyclosporine A was stopped 6 months after the second transplantation, and prednisolone and azathioprine were stopped 6 months later. After the occurrence of acute graft rejection and the identification of human leucocyte antigen (HLA) antibodies in 30% of the patients tested,[23] guided by international experts in immunology, we established a new immunosuppression protocol for the last 20 patients. This involved monitoring HLA antibodies at each center and prolongation of full immunosuppression for up to 1 year after the second graft. Azathioprine and prednisolone were continued for 6 additional months, and prednisolone was withdrawn gradually. Plasma HLA antibodies were then monitored locally at each hospital, and treatment was modified (withdrawal of cyclosporine or of prednisolone) on occurrence of any unusual signs. Oral immunosuppressive therapy was withdrawn if no HLA antibodies against the grafts were detected.

Short and full assessments were alternated for clinical examination (Fig. S1). We used the complete UHDRS, cognitive tasks,[24] back-and-forth hand-tapping, and electrophysiological assessments. When surgery could not be done on the scheduled date because of a lack of fetus availability, preoperative assessments were repeated if the interval between them and the transplant exceeded 3 months. Brain imaging included MRI, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), and, in patients not on neuroleptics, with ^{11}C-raclopride PET (Supplementary Methods).

Endpoints

The primary outcome was the UHDRS-TMS compared between treatment and control groups at 20-month postrandomization (M32). TMS is a composite score for chorea, dystonia, oculomotor movement, tapping, pronation/supination, palm/hand/fist sequence task, walking, tongue protrusion, and rigidity, rated from 0 to 124 points, with higher scores indicating poorer performance. Secondary outcomes included clinical, imaging, and electrophysiological findings as well as comparison of pregraft and postgraft TMS slopes during the entire study period (M0–M52) regardless of the time of transplant. Adverse events (AEs) were identified on clinical examination, according to the World Health Organization checklist, at all visits and between visits if spontaneously reported by patients (Table S1).

Statistical Analysis

Sample size calculation relied on data from an observational cohort of patients with early HD comparable with those included in the present trial and followed for up to 4 years,[24] showing an average annual natural progression of +13.2 ± 14.1 for the UHDRS-TMS. Hypothesizing a stable evolution as a clinically meaningful effect of the graft, inclusion of ≥18 subjects per group was required to achieve 80% power at a 2-sided 5% α level. To account for a prespecified subgroup analysis led in graft recipients with a metabolically active transplant based on FDG PET imaging (60% expected as in reference 11), a sample size of 60 (30 per group) was targeted.

For the primary outcome, patients were assessed according to randomized group under the modified intent-to-treat principle, including all patients from the control group and patients from the treatment group having received a transplant. The main planned primary endpoint analysis relied on the comparison of the TMS at M32 between treatment and control groups using analysis of covariance (ANCOVA) of the score at M32 with the initial value at M12 as a covariate. Supportive sensitivity analyses of the primary endpoint included: (1) ANCOVA with further adjustment for center and other covariates at M12 with prognostic value or showing evidence of a potential imbalance between study arms at the time of randomization and/or transplant, (2) comparison of the absolute change in TMS from M12 to M32 between the 2 randomized groups, and (3) assessment of the graft effect on the evolution of TMS over time (M0–M52) regardless of the randomized group using a piecewise 2-part (before–after the first transplant) linear mixed model.

Clinical and electrophysiological secondary endpoints were compared between randomized groups using ANCOVA of values at M32 with values at M12 as a covariate, adjusting for similar covariates as for the primary outcome, with the addition of the TMS. Potential effect modifiers that could predict improved response to intrastriatal transplant were searched for from a preselected list of 21 variables relating to patients and intervention by testing for interactions between time after first graft and the candidate predictors in a piecewise linear mixed model (Supplementary Methods).

All tests were 2-tailed, with $P < 0.05$ considered significant. Analyses were prespecified in the trial protocol and

performed with Stata v15.1 (StataCorp, College Station, TX) and R-3.6.0 (R Foundation, Vienna, Austria).

Following the discovery of immune rejection,[23] detection of antibodies directed against HLA class I and class II antigens expressed by donor tissues was assessed in each center using the locally available technique.

MRI Analyses

MRI was planned as part of the study design for safety only. We conducted a retrospective volumetric segmentation analysis using the Freesurfer software in patients scanned on the same machine for PET coregistration (Supplementary Methods).

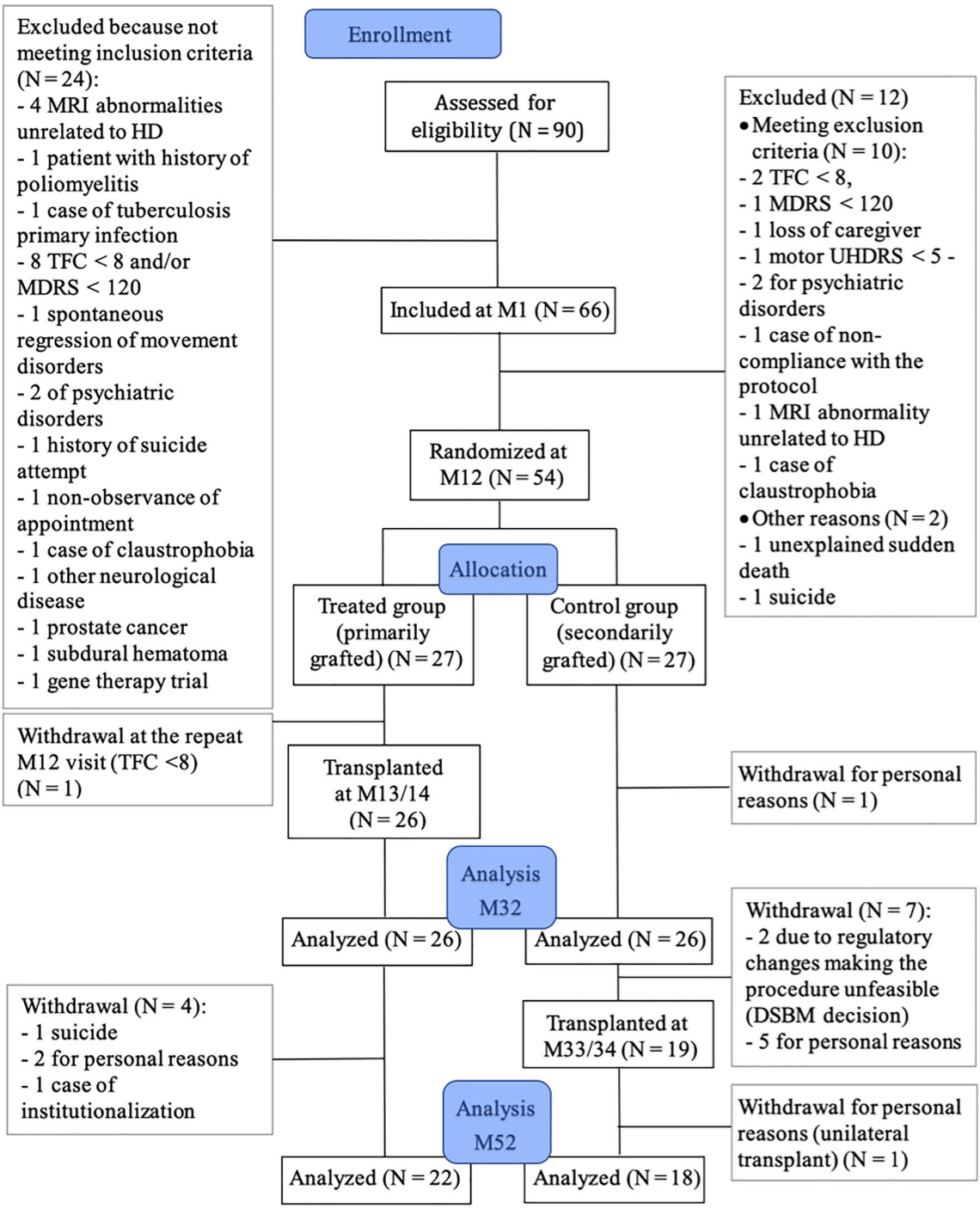

FIG. 1. Participant flow chart. At the end of the study, 41 patients had undergone bilateral transplantation, and 4 had undergone unilateral transplantation. DSMB, Data and Safety Monitoring Board; HD, Huntington's disease; MDRS, Mattis Dementia Rating Scale; M1, month 1; M12, month 12; M13, month 13; M14, month 14; M33, month 33; M34, month 34; MRI, magnetic resonance imaging; TFC, total functional capacity; UHDRS, Unified Huntington's Disease Rating Scale.

Results

Between January 2001 and May 2006, 66 patients met the inclusion criteria (M0–M1), 54 were randomized (M12), and 45 underwent transplantation (treatment group, 24 bilateral and 2 unilateral; and controls secondarily grafted, 17 bilateral and 2 unilateral) (Fig. 1). Unilateral implantations were the result of

TABLE 1. Demographic and baseline characteristics of patients both at inclusion and at randomization

Patients' Characteristics and Assessments	Included Patients, M0 Total N = 54	Randomized Patients, M12		
		Treated N = 27	Control N = 27	*P* Value
Age, y, mean ± SD	43.3 ± 8.7	43.2 ± 9.2	46.2 ± 8.4	0.226
Sex, n (%)				
Male	34 (63.0)	18 (66.7)	16 (59.3)	0.573
Female	20 (37.0)	9 (33.3)	11 (40.7)	
Education, y, mean ± SD	12.2 ± 3.3	11.6 ± 3.1	12.7 ± 3.5	0.227
Inheritance of HD, n (%)				
Father	32 (59.3)	17 (63.0)	15 (55.6)	0.460
Mother	21 (38.9)	9 (33.3)	12 (44.4)	
Unknown	1 (1.9)	1 (3.7)	0 (0.0)	
CAG repeat length, median (IQR)	44.5 (43.0–47.0)	45.0 (44.0–48.0)	44.0 (42.0–46.0)	0.119
Disease duration, y, mean ± SD	6.0 ± 2.9	7.1 ± 3.0	4.9 ± 2.3	**0.004**
Letter fluency (1 minute), mean ± SD	25.7 ± 9.0	26.6 ± 12.5	28.0 ± 8.2	0.609
Letter fluency (2 minutes), mean ± SD	38.3 ± 15.3	37.1 ± 18.8	41.9 ± 13.8	0.285
Symbol Digit Modality Test, mean ± SD	27.3 ± 8.2	23.0 ± 7.9	25.0 ± 8.8	0.391
Stroop Word, mean ± SD	67.5 ± 15.5	61.1 ± 17.1	65.4 ± 17.0	0.367
Stroop Color, mean ± SD	48.8 ± 10.6	45.6 ± 11.8	48.0 ± 14.8	0.525
Stroop interference word/color, mean ± SD	27.6 ± 8.4	27.4 ± 9.8	26.9 ± 9.6	0.834
Total Motor Score, mean ± SD	29.4 ± 12.5	38.0 ± 14.4	31.4 ± 12.4	0.078
Total functional capacity, mean ± SD	11.7 ± 1.0	10.6 ± 1.5	11.0 ± 1.3	0.252
Independence Scale, mean ± SD	91.9 ± 7.0	86.3 ± 7.7	88.0 ± 8.6	0.455
Functional Assessment Scale, mean ± SD	26. ± 1.4	27.9 ± 1.8	27.0 ± 1.6	0.053
Behavior, mean ± SD	12.9 ± 8.7	9.7 ± 7.1	10.8 ± 9.2	0.610
Mattis Dementia Rating Scale, mean ± SD	132.4 ± 6.7	129.9 ± 7.2	130.3 ± 6.8	0.832
Categorical fluency, mean ± SD				
1 Minute	13.9 ± 3.9	12.9 ± 4.1	14.3 ± 3.4	0.165
2 Minutes	21.3 ± 6.1	19.6 ± 6.7	22.1 ± 6.3	0.167
Figure cancellation, mean ± SD				
1 Figure	32.6 ± 11.2	28.9 ± 9.3	36.2 ± 11.9	**0.015**
2 Figures	33.0 ± 11.3	29.9 ± 9.8	36.2 ± 13.2	0.050
3 Figures	25.4 ± 11.5	24.4 ± 9.7	28.0 ± 11.5	0.221
Hopkins Verbal Learning Task, mean ± SD				
Immediate recall	20.6 ± 5.4	18.7 ± 4.3	18.4 ± 4.9	0.793
Delayed recall	6.5 ± 3.0	6.2 ± 2.3	5.7 ± 2.6	0.407
Recognition	10.4 ± 1.6	10.2 ± 1.5	9.9 ± 2.1	0.609
Trail-Making Test, mean ± SD				
Part A (seconds)	73.4 ± 30.8	82.1 ± 38.3	78.8 ± 37.9	0.752
Part B (seconds)	145.0 ± 60.8	150.7 ± 57.1	159.6 ± 70.5	0.611
Montgomery and Asberg Depression Rating Scale, mean ± SD	9.2 ± 6.5	9.1 ± 6.6	8.8 ± 6.9	0,869
Articulatory speeds	7.1 ± 2.0	7.4 ± 2.5	7.0 ± 1.7	0.531
Back-and-forth hand-tapping, mean ± SD				
Right	26.3 ± 9.0	28.6 ± 9.5	25.4 ± 8.0	0.219
Left	28.1 ± 10.2	32.8 ± 11.9	27.1 ± 7.7	0.061
Electrophysiology, mean ± SD				
R2 right (ms)	37.0 ± 5.3	39.0 ± 5.9	37.8 ± 6.5	0.558
R2 left (ms)	35.2 ± 3.4	37.4 ± 4.4	38.0 ± 6.0	0.744
N20 right (μV)	0.7 ± 0.7	0.8 ± 0.9	1.1 ± 1.2	0.328
N20 left (μV)	0.9 ± 0.9	0.9 ± 0.7	0.9 ± 1.0	0.742
N30 right (μV)	0.5 ± 1.1	0.6 ± 0.7	0.7 ± 1.0	0.751
N30 left (μV)	0.4 ± 0.7	0.8 ± 0.8	0.7 ± 1.2	0.770

M0, month 0; M12, month 12; SD, standard deviation; CAG, cytosine-adenine-guanine; IQR, interquartile range; R2, second response of the blink reflex to supraorbital nerve stimulation; N20, parietal component of the somatosensory evoked potentials to median nerve stimulation ("negative" peak at around 20 ms latency); N30, frontal component of the somatosensory evoked potentials to median nerve stimulation ("negative" peak at around 30 ms latency).
Bold values are indicates that demographics and baseline are presented at month 0 when patients were included in the run in period, and then at month 12, at the moment they were randomized.

cancellation of the contralateral transplantation following serious surgical complications after the first transplant in 2 patients and to the decision of 2 others not having a second transplant following several cancellations of surgery as a result of insufficient tissue collection. Demographic and baseline characteristics are shown in Table 1. Patient demographic and clinical characteristics were not significantly different between the 2 groups at the M12 randomization timepoint, except for a longer disease duration and a more severe 1-figure cancellation task for the treatment group. Median follow-up was 56.9 months (interquartile range, 54.5–64.1) for the treatment group and 60.0 months (interquartile range, 56.6–65.7) for controls.

Safety

We recorded 287 AEs from M0 to M52 in the 54 randomized patients during a period of 12 years (Table S1); 91% were not attributed to the procedure, and 9% were related to the procedure (immunosuppressant or transplant). Among those, there were 27 SAEs, of which 17

TABLE 2. Comparisons between randomized groups in adjusted changes from M12 to M32 for the primary and secondary endpoints

	Control			Treated			
Assessments	M12	M32	Change M12–M32	M12	M32	Change M12–M32	*P* Value*
Total motor score	33.3 ± 2.7	42.6 ± 2.1	8.1 ± 2.1	35.9 ± 3.0	44.8 ± 2.3	10.3 ± 2.3	0.520
Letter fluency (1 minute)	27.3 ± 1.8	26.0 ± 1.7	−1.2 ± 1.5	29.8 ± 2.0	24.9 ± 1.9	−4.9 ± 1.7	0.138
Letter fluency (2 minutes)	40.8 ± 2.9	38.9 ± 2.4	−1.9 ± 2.5	41.7 ± 3.2	34.2 ± 2.7	−7.5 ± 2.8	0.172
Symbol Digit Modality Test	23.4 ± 1.5	20.6 ± 1.3	−2.9 ± 1.2	26.8 ± 1.7	20.8 ± 1.5	−6.0 ± 1.3	0.101
Stroop word	60.7 ± 2.6	59.2 ± 3.1	−1.5 ± 2.8	68.1 ± 2.9	54.9 ± 3.5	−13.2 ± 3.1	**0.013**
Stroop color	44.7 ± 2.4	39.6 ± 2.2	−5.1 ± 2.1	49.4 ± 2.7	45.8 ± 2.4	−3.6 ± 2.4	0.654
Stroop interference word/color	25.1 ± 2.0	22.6 ± 1.7	−2.5 ± 1.1	29.1 ± 2.2	25.4 ± 1.9	−3.7 ± 1.3	0.521
Total functional capacity	11.0 ± 0.2	9.1 ± 0.4	−1.9 ± 0.5	11.0 ± 0.2	8.9 ± 0.5	−2.1 ± 0.5	0.771
Independence Scale	87.8 ± 1.5	81.5 ± 1.9	−6.4 ± 1.9	87.9 ± 1.7	78.5 ± 2.2	−9.4 ± 2.2	0.347
Functional Assessment Scale	27.2 ± 0.3	29.5 ± 0.7	2.3 ± 0.7	27.2 ± 0.3	30.5 ± 0.8	3.3 ± 0.8	0.374
Behavior	10.5 ± 1.8	9.8 ± 1.7	−0.7 ± 1.7	9.8 ± 2.0	9.1 ± 1.9	−0.7 ± 1.9	0.981
Mattis Dementia Rating Scale	128.6 ± 1.2	125.0 ± 1.6	−3.6 ± 1.4	131.6 ± 1.4	127.7 ± 1.8	−3.8 ± 1.6	0.923
Categorical fluency (1 minute)	13.5 ± 0.7	12.2 ± 0.8	−1.3 ± 0.9	13.5 ± 0.8	11.5 ± 0.9	−2.0 ± 1.0	0.623
Categorical fluency (2 minutes)	21.1 ± 1.2	19.0 ± 1.1	−2.1 ± 1.2	21.2 ± 1.4	17.8 ± 1.2	−3.4 ± 1.3	0.506
Figure cancellation 1-figure	36.1 ± 2.2	29.4 ± 1.5	−3.7 ± 1.5	29.5 ± 2.4	25.1 ± 1.7	−8.0 ± 1.7	0.092
Figure cancellation 2-figures	34.6 ± 1.4	28.5 ± 1.6	−6.1 ± 1.4	35.5 ± 1.6	25.7 ± 1.8	−9.7 ± 1.5	0.112
Figure cancellation 3-figures	27.7 ± 1.9	23.1 ± 1.9	−4.6 ± 1.7	28.6 ± 2.1	20.2 ± 2.2	−8.3 ± 1.9	0.186
Hopkins Verbal Learning Task, immediate recall	18.2 ± 1.0	18.3 ± 1.2	0.2 ± 0.9	18.4 ± 1.1	19.3 ± 1.3	0.9 ± 1.0	0.637
Hopkins Verbal Learning Task, delayed recall	5.7 ± 0.6	6.3 ± 0.7	0.6 ± 0.6	6.1 ± 0.7	6.2 ± 0.8	0.1 ± 0.6	0.606
Hopkins Verbal Learning Task, recognition	10.2 ± 0.5	10.1 ± 0.4	−0.2 ± 0.4	10.1 ± 0.5	10.3 ± 0.4	0.2 ± 0.5	0.606
Trail-Making Test part A (seconds)	78.6 ± 5.4	100.6 ± 8.6	22.0 ± 6.1	72.1 ± 6.0	97.2 ± 9.6	25.1 ± 6.8	0.751
Trail-Making Test part B (seconds)	168.0 ± 11.7	180.7 ± 12.5	12.8 ± 8.4	141.3 ± 13.0	178.9 ± 14.0	37.6 ± 9.4	0.076
Montgomery and Asberg Depression Rating Scale	10.1 ± 1.6	7.5 ± 1.8	−2.6 ± 1.4	7.5 ± 1.8	8.8 ± 2.0	1.3 ± 1.5	0.095
Articulatory speed (seconds)	7.4 ± 0.4	7.9 ± 0.4	0.4 ± 0.3	6.6 ± 0.5	7.5 ± 0.4	0.9 ± 0.4	0.372
Back-and-forth hand-tapping right	26.3 ± 1.8	26.7 ± 1.5	0.3 ± 1.2	24.5 ± 1.9	26.9 ± 1.6	2.3 ± 1.3	0.300
Back-and-forth hand-tapping left	27.9 ± 1.9	29.4 ± 1.9	1.6 ± 1.5	27.0 ± 2.0	31.7 ± 2.0	4.8 ± 1.6	0.179
R2 right (ms)	38.3 ± 1.6	38.5 ± 1.5	0.2 ± 1.5	38.1 ± 1.7	38.9 ± 1.6	0.8 ± 1.6	0.792
R2 left (ms)	38.1 ± 1.4	39.0 ± 1.8	0.9 ± 1.2	38.0 ± 1.5	39.6 ± 2.0	1.6 ± 1.3	0.710
N20 right (μV)	0.9 ± 0.3	0.8 ± 0.2	−0.1 ± 0.2	0.7 ± 0.3	0.7 ± 0.2	−0.1 ± 0.2	0.880
N20 left (μV)	0.9 ± 0.2	1.0 ± 0.2	0.1 ± 0.2	0.8 ± 0.2	0.6 ± 0.3	−0.2 ± 0.2	0.237
N30 right (μV)	0.9 ± 0.3	0.5 ± 0.2	−0.4 ± 0.2	0.4 ± 0.3	0.5 ± 0.2	0.1 ± 0.2	0.095
N30 left (μV)	0.8 ± 0.2	0.5 ± 0.2	−0.4 ± 0.2	0.4 ± 0.2	0.6 ± 0.2	0.2 ± 0.2	0.129
TEP (N voxels in the striatum)	1086 ± 88	1208 ± 85	121 ± 57	1171 ± 98	1316 ± 95	145 ± 64	0.798

Results are adjusted means ± standard error.
*Comparison of changes from M12 to M32 after adjustment for M12 values of Total Motor Score, figure cancellation 1-figure, categorical fluency (1 minute), Independence Scale, Functional Assessment Scale, and disease duration.
M12, month 12; M32, month 32; R2, second response of the blink reflex to supraorbital nerve stimulation; N20, parietal component of the somatosensory evoked potentials to median nerve stimulation ("negative" peak at around 20 ms latency); N30, frontal component of the somatosensory evoked potentials to median nerve stimulation ("negative" peak at around 30 ms latency); TEP, positron emission tomography.
Bold value indicates that demographics and baseline are presented at month 0 when patients were included in the run in period, and then at month 12, at the moment they were randomized.

were considered unrelated to the procedure: 1 death by suicide, 2 suicide attempts, 3 fractures, 1 road accident, 1 acute fever, 2 gastrointestinal disorders, 1 pulmonary embolism, and 6 hospitalizations for psychiatric disorders. A total of 10 SAEs were procedure related: 1 intracranial empyema, 3 SDHs (2 requiring surgical drainage), 1 putaminal hematoma resulting in hemiparesis and aphasia, 1 seizure, 1 graft rejection,[23] and 3 intrastriatal cysts. As a result of progressive cranial hypertension, 1 of these patients with an intragraft cyst required cauterization of aberrant choroid plexus within the graft. Following this, the patient improved clinically and in terms of his striatal metabolism (ipsilateral to the cyst) compared to presurgery. Surgical and postoperative procedures were modified to prevent further hematomas in the following 57 grafts, leading to significant improvement (Fisher's test $P = 0.03$).

Despite cyclosporine monitoring and dose titration, 18 of the 43 patients tested (39 during the 52-month study and 4 subsequently) were positive for HLA antibodies. We did not find correlation between the clinical results and the presence of HLA antibodies.

Efficacy

M32 TMS scores did not differ significantly between treatment (50.8 ± 17.3, N = 26) and control groups (39.0 ± 17.0, N = 26; ANCOVA adjusted for M12, $P = 0.31$; adjusted difference in means +2.9, 95% confidence interval [95% CI], −2.8 to 8.6). This was confirmed by supportive analyses after adjustment for disease duration ($P = 0.54$), center ($P = 0.30$), or multiple adjustment for both and other potentially influent covariates (ie, Independence Scale, Functional

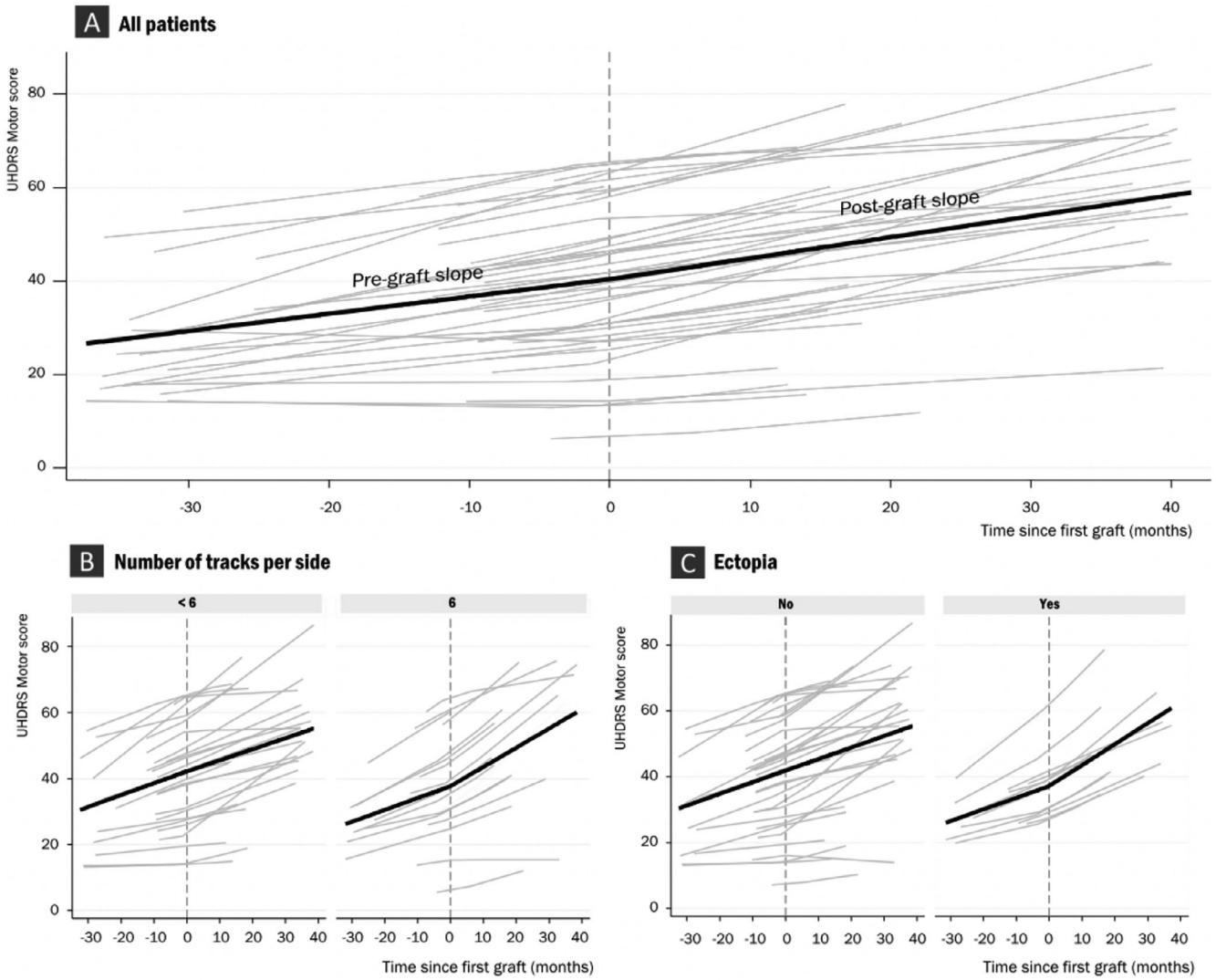

FIG. 2. Changes in UHDRS motor score in individual patients after the first transplant: results for the whole study population (**A**) and as a function of ectopia (**B**) and number of tracks per side (**C**). The black line shows the estimated progression of the Multicentric Intracerebral Grafting in Huntington's Disease cohort through the piecewise linear mixed model over the pregraft and postgraft time periods. M12, month 12; M32, month 32; UHDRS, Unified Huntington's Disease Rating Scale.

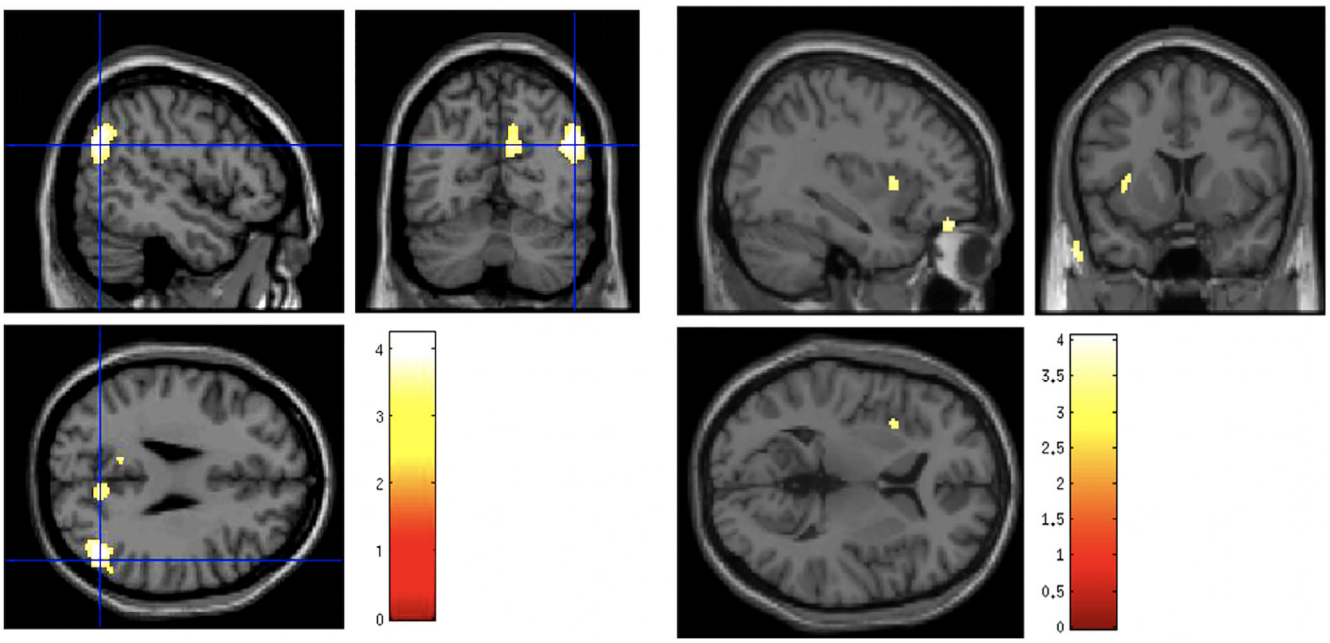

FIG. 3. Statistical parametric mapping analysis at month 32 comparing the treated patients and the control not yet treated groups at ^{18}F-fluorodeoxyglucose scans. Regions in which changes in metabolism relative to the month 12 baseline differed significantly between the treated group and control not yet treated group at month 32 ($P < 0.001$). These regions, overlaid on a T1-weighted brain magnetic resonance imaging scan, correspond to the right angular gyrus and precuneus. Left: higher metabolism in the right angular cortex and precuneus in the treated patients. Right: lower metabolism in the left insula in the treated patients. No significant difference was observed in the striatum.

Assessment Scale, 1-figure cancellation, categorical fluency [1 minute]; $P = 0.68$), and in comparisons of mean absolute TMS change from M12 to M32 (+10.3 ± standard error 2.3 [treatment] vs. +8.1 ± 2.1 [controls], $P = 0.52$; Table 2). A longitudinal analysis of graft effect on TMS, regardless of group randomization, found no difference between the pregraft and postgraft progression slopes (piecewise linear mixed model, $P = 0.65$; Fig. 2A). The reliability of clinician-rated TMS, assessed by blind scoring on the 96 exploitable videos from M12 to M52, was excellent (intraclass correlation coefficient = 0.92 with 95% CI, 0.88–0.94; $P < 0.001$; Fig. S2).

No significant striatal metabolic differences were observed in FDG PET scans between M12 and M32 in either treated (N = 26) or control (N = 19; Fig. 3) patients. At M32, 8 treated patients showed a nonsignificant lower number of hypometabolic striatal voxels compared with M12 (means M12, 1519.3 ± 395.9; M32, 1308.0 ± 315.1). Their TMS (mean 49.8 ± 10.7) was similar with that of control patients (ANCOVA adjusted for M12, $P = 0.46$). As for clinical and electrophysiological secondary endpoints, no statistically significant differences were found between randomized groups between M12 and M32 adjusted for potentially confounding covariates (ie, M12 values of TMS, 1-figure cancellation, categorical fluency [1 minute], Independence Scale, Functional Assessment Scale, and disease duration), except for Stroop word showing a more severe decrease in the treated than in the control group (Table 2).

Analyses of basal ganglia MRI volumes between M12 and M32 showed a significant increase of the striatal volume in treated patients (N = 13) compared with controls (N = 16; $P < 0.001$) without correlation with clinical scores (Supplementary Methods).

Exploratory analyses were performed on 10 parameters characterizing the patients' pattern and 11 procedural aspects to identify potential predictors of transplantation outcome (Supplementary Methods). Interaction analyses in the longitudinal linear mixed model detected 2 detrimental predictors of steeper decline in postgraft TMS: ectopia (interaction term −0.29; 95% CI, −0.58 to −0.002; $P = 0.049$) and a trend for a high number of tracks per side ≤5.5 (interaction term −0.25; 95% CI, −0.51 to 0.047; $P = 0.067$; Fig. 2B,C).

Discussion

This randomized, multicenter, delayed-start phase II trial was designed to assess the safety and efficacy of the intrastriatal transplantation of human fetal cells in 54 patients in early to moderate stages of HD, of whom 45 were eventually grafted. A comparison of the treatment (N = 26) and control groups (N = 19) at M32 showed no improvement in TMS, even after restricting the analysis to the treated patients identified as having an increased striatal metabolism on FDG PET imaging. TMS slope was unaffected by transplantation. No

benefit for secondary outcomes was observed (Table 2). We observed no increase in raclopride binding, suggesting no/little increase in striatal-like tissue, and no metabolic improvement in the striatum or frontal cortex posttransplantation in 80% of the grafted patients.[25] This may have been the result of implantation of insufficient quantities of tissue or poor tissue survival for a range of reasons including graft rejection, the latter according with the demonstration of transplant alloimmunogenicity[23] in 41% patients tested for HLA antibodies.

Human fetal cells dissected from the developing striatum are theoretically good donor cells for transplantation in patients with HD, but their availability is limited. This limitation necessitated a long study period (2001–2013), but did not affect the planned analyses, with repeated assessments for the comparison of treated and control (secondarily transplanted) patients. The high degree of consistency of blinded and investigator-attributed TMS scores demonstrates robustness (but possibly also insensitivity) of TMS scoring. Of note, an imbalance in TMS values at M12 was apparent between controls and treated patients despite randomization. This observation most likely did not affect our findings based on between-groups comparisons adjusted for M12 values, with comparable results found in the longitudinal analysis of TMS in all grafted patients, regardless of initial group allocation.

Deaths occurred even before randomization (Fig. 1), highlighting the fragility of patients with HD. Where appropriate, protocol adaptations were made during the study to address AEs, improve patient safety, and prevent transplantation-related SAEs (see Methods), without modifying the statistical validity of the trial. The initial surgical procedure, which resulted in SDH or putaminal hematoma in 10% of transplant recipients, compared favorably with the 43% reported in some pilot studies of fetal cell transplantation in HD.[14] This risk was eliminated by omitting the 2 posterior tracks in patients with marked atrophy, hyperhydrating patients and imposing 48 hours bed rest; no such events occurred in the subsequent 57 surgical implantations. We also successfully treated an expanding choroid cyst within the graft by endoscopic cauterisation of choroid cells. This strategy would likely be of value for future stereotaxic surgical trials.

Only a few studies have reported unequivocal long-lasting transplant success, and little is known about the factors underlying graft failure.[10] Graft–host connectivity has been demonstrated,[15] but previous studies in small cohorts of patients were unable to identify the key factors influencing transplant outcome.[14,26-30] The MIG-HD trial, with 45 grafted patients at 6 centers, will help to advance cell transplantation practices for HD by identifying some key factors that need to be considered in future studies. The transition from single centre to multicenter settings resulted in greater variability between the centers than anticipated, particularly for surgery-related factors, resulting in substantial graft variability across the study. For example, larger numbers of injection tracks were expected to improve graft function, but our results suggest in contrast that slower deterioration of the TMS was associated with lower number of tracks. This observation might result from a combination of the number of fetuses (from 1 to 2), presence of HLA antibodies, patients' sex, and duration of surgery, even if not proven statistically in these few individuals. It was unclear in the study by Paganini and colleagues[30] whether ectopic grafts had a negative impact on graft function. In a blind analysis of MRI images, we show here that TMS deteriorated more in patients with ectopic transplants. Although we did not find any correlation between striatal volume change measured using MRI and clinical evolution, recent MRI techniques should constitute a key marker in future trials.[3] In contrast, given the difficulty to avoid neuroleptic intake in HD, alternative tracers in future longitudinal long-term studies should replace ^{11}C-raclopride PET imaging. The number of hypometabolic striatal voxels correlated with TMS on FDG PET scans, without allowing us to detect clinically responsive patients. This lack of consistent correlation of imaging and clinical response reproduces the results of other studies also reporting alloimmunization processes against the graft.[29,31] It might be the case that chronic inflammation attributed to alloimmunization and transplant variability blurred the picture. Alloimmunization[23] was unpredictable, and changes in detection techniques during MIG-HD made it impossible to model the impact of HLA antibodies. Compared with our pilot trial,[11] the use of older fetuses, the pooling of ganglionic eminences from several fetuses to increase graft volume, and the reduction of the intergraft interval from 1 year to about 2 months may have increased the risk of alloimmunization. Here, 40% of patients developed HLA antibodies against the graft. In contrast, none of our patients from the pilot trial, with 1-year intervals between transplants, had antibodies against the transplant 5 years after surgery (unpublished data). In 2 studies with short intergraft intervals (2–7 months), HLA antibodies were present in 50% of patients in the German branch of MIG-HD[29] and 37.5% in the Firenze study.[31] The results of the MIG-HD study suggest that better standardization and control of procedures, with improvements in atrophic structure targeting and cell injection methods, are required for future transplant studies. It should be possible to decrease the numbers of ectopic grafts and injection tracks, but it will be harder to control HLA antibody development. These antibodies were also present in patients on immunosuppressants despite a correct cyclosporine titration, suggesting suboptimal

immunosuppression protocol. Yet, establishing the link between presence of HLA antibodies against the graft and its lack of functionality is difficult because, except in the case of acute rejection,[23] alloimmunization appears to be a long process. However, functional impact of alloimmunization, reported in monkeys,[32] justifies better procedures to avoid alloimmunization in future studies. The future use of stem cell–derived neural precursors should resolve many of the critical issues highlighted here, improving surgical intervention planning and facilitating the use of well-defined homogeneous cell therapy products effectively matched with the patient's characteristics in advance. There are also some factors not considered here, such as tissue preparation,[33,34] which could be addressed in further studies. In retrospect, the outcome measures lacked sensitivity (see reference 35), which calls for new sensitive digitalized measures, as developed in the RepairHD program.

In summary, it could be concluded that grafts cannot restore the frontostriatal circuits despite the positive abundant animal literature,[18] but we think that it would be premature to conclude this based on the MIG-HD study, which has highlighted many important questions that need to be addressed. It would also be premature to disregard the results of our previous pilot study, in which striking clinical improvement was seen in 3 patients across multiple outcomes analyzed blindly to each other (clinics PET, electrophysiology, and digitalized movement analysis), including an increase of the metabolism in the frontal cortex,[13,25,27] together constituting a proof of concept. We thus believe that a rational approach is to return to the bench to solve the issues raised here; if that can be achieved there may be a place for intracerebral transplantation, which is the only approach currently available with the potential to reverse the loss of striatal tissue. We propose that the lessons learned from MIG-HD could guide future transplant trials, whether for HD or other neurodegenerative diseases. ■

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Anne-Catherine Bachoud-Lévi, the principal investigator of MIG-HD, supervised all aspects of the study and was responsible for neurological and neuropsychological training. Drs. Catherine Schramm, Christophe Lalanne, and Renaud Massart curated the data. They ran the analyses with Prof. Etienne Audureau. The principal investigators at the various centers were Christophe Verny and Prof. Philippe Menei (Angers); Dr. Clemence Simonin, Prof. Pierre Krystkowiak, and Prof. Serge Blond (Lille/Amiens); Dr. Frédéric Supiot and Prof. Marc Levivier (Brussels); Prof. Jean-François Démonet and Prof. Jean-Christophe Sol (neurosurgeon co–principal investigator; Toulouse); Prof. Philippe Damier (Nantes). Dr. Marc Peschanski and Dr. Philippe Hantraye supervised cell therapy and Prof. Stéphane Palfi supervised surgery (Créteil, neurosurgeon principal investigator); Prof. Philippe Remy, Dr. Véronique Gaura, and Sonia Lavisse supervised the positron emission tomography scans; Drs. Pierre Brugières and Laurent Cleret de Langavant supervised magnetic resonance imaging and analyzed the data obtained; Prof. Bassam Haddad and Dr. Roland Jeny were responsible for obstetric supervision; Dr. Patrick Maison was responsible for methodology; and Prof. Jean-Pascal Lefaucheur supervised the electrophysiology studies. Amandine Rialland and David Schmitz participated in data curation and administrative supervision, Dr. Dominique Challine oversaw the viral work, and Prof. Anne Rosser was responsible for blind videoscoring.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.