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Human fetal cell therapy in Huntington's disease: a randomized, multicenter, phase II trial (MIG-HD)

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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 with 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 M12 to either the treatment group (transplanted at M13-M14) or the control group, secondarily treated 20 months later (M33-M34). The primary outcome was total motor score compared between both groups at 20-month post-randomization (M32). Secondary outcomes included clinical, imaging and electrophysiological findings, and comparison of pre- and post-graft total motor score slopes over the whole study period (M0-M52) 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 M32 did not differ between groups (treated-controls difference in means adjusted for M12: +2.9 [CI95 -2.8 to 8.6]; P=0.31). Its rate of decline after transplantation was similar to that before transplantation. 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 anti-Human Leucocytes Antigen antibodies in 40% of 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.

INTRODUCTION

HD is a rare inherited neurodegenerative disorder, which 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 (QA) 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 non-human primate QA 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 (e.g.[8,9]). Since the 1990s, 70 HD patients[10] have been enrolled in open-label, non-randomized, 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] Graft-host connection was demonstrated in post mortem 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 M0 or 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 six French and Belgian hospitals between 2001 and 2010; their follow-up to M52 was completed in 2013. The main inclusion criteria were: having manifest HD for ≥1 year, >36 CAG repeats in the huntingtin gene, age 18-65 years, total motor score (TMS) >5 on the Unified Huntington's Disease Rating Scale (UHDRS), and total functional capacity (TFC) score >9. The main exclusion criteria were: Mattis Dementia Rating Scale (MDRS) score <120, and contraindication for surgery or magnetic resonance imaging (MRI) (**supplementary methods**).

Randomization and masking

After a one-year run-in period, designed to verify patients' compliance and exclude unusual patterns of clinical deterioration, patients were randomly assigned at month 12 (M12) in a 1:1 ratio either to treatment (receiving transplant at M13-M14) or to the (initially untreated) control group, which were subsequently grafted 20-months later (M33-M34) (**Figure S1**). Randomization was computer-generated, with centralized allocation concealment. A randomisation list prepared at the Henri Mondor Clinical Research Unit with Nquery software (Statistical Solutions Ltd., Boston, USA) 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, M32 and M52 and scored by specialists not involved in patient follow-up and recruitment and blind to treatment allocation (**Figure S2**).

Procedures

Small blocks of whole ganglionic eminences from one to three 8.5- 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 six tracks (mean 4.91±1.46; range 3 to 6) within the head of the caudate nucleus (pre-commissural and commissural) and the putamen (one in each of pre-commissural and commissural, and two in post-commissural putamen). This totalled 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 centres. 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 h after surgery.

Immunosuppression was achieved with cyclosporine A, beginning three 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 six months after the second transplantation, and prednisolone and azathioprine were stopped six months later. After the occurrence of acute graft rejection and the identification of Human Leucocytes 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 centre and prolongation of full immunosuppression for up to one year after the second graft. Azathioprine and prednisolone were continued for six 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 (**Figure 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 due to lack of foetus availability, preoperative assessments were repeated if the interval between them and the transplant exceeded three months. Brain imaging included MRI, ^{18}F-fluorodeoxyglucose PET (FDG-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 post-randomization (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 pre- and post-graft TMS slopes over the whole 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 early HD patients comparable to 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% alpha level. To account for a prespecified subgroup analysis led in graft recipients with a metabolically active transplant based on FDG-PET imaging (60% expected like in [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: i) ANCOVA with further adjustment for centre 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; ii) comparing the absolute change in TMS from M12 to M32 between the two randomized groups and iii) assessing the graft effect on the evolution of

TMS over time (M0-M52) regardless of the randomized group using a piecewise two-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 total motor score. 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 two-tailed, with $P<0.05$ considered significant. Analyses were prespecified in the trial protocol and performed with Stata v15.1 (StataCorp, College Station, USA) 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**).

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) (**Figure 1**). Unilateral implantations were due to cancellation of the contralateral transplantation following serious surgical complications after the first transplant in two patients, and to the decision of two others not having a second transplant following several cancellations of surgery due to insufficient tissue collection. Demographic and baseline characteristics are shown in **Table 1**. Patient demographic and clinical characteristics were not significantly different between the two groups at the M12 randomization time point, 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 [IQR] 54.5-64.1) for the treatment group, and 60.0 months (IQR 56.6-65.7) for controls.

Safety

We recorded 287 AEs from M0 to M52 in the 54 randomized patients over a period of 12 years (**Table S1**); 91% were not attributed to the procedure and 9% related to the procedure (immunosuppressant or transplant). Among those, there were 27 SAEs, of which 17 were considered unrelated to the procedure: one death by suicide, two suicide attempts, three fractures, one road accident, one acute fever, two gastrointestinal disorders, one pulmonary embolism, and six hospitalizations for psychiatric disorders. Ten SAEs were procedure-related: one intracranial empyema, three SDHs (two requiring surgical drainage), one putaminal hematoma resulting in hemiparesis and aphasia, one seizure, one graft rejection,[23] and three intrastriatal cysts. Due to progressive cranial hypertension, one of these patients with an intra-graft cyst required cauterisation 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 pre-surgery. 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, eighteen of the 43 patients tested (39 during the 52-month study and four 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 [CI95 -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 (i.e. independence scale, functional assessment scale, 1-figure cancellation, categorical fluency (1 min.); 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 pre-graft and post-graft progression slopes (piecewise linear mixed model, P=0.65; **Figure 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] and P<0.001) (**Figure 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; **Figure 3**) patients. At M32, eight treated patients showed a non-significant lower number of hypometabolic striatal voxels compared to M12 (means M12: 1519.3±395.9 and M32: 1308.0±315.1). Their TMS (mean 49.8±10.7) was similar to 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 (i.e. M12 values of total motor score, 1-figure cancellation, categorical fluency (1 min.), 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 to 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 two detrimental predictors of steeper decline in post-graft TMS: ectopia (interaction term -0.29 [CI95% -0.58 to -0.002], P=0.049) and a trend for high number of tracks per side ≤5.5 (-0.25 [-0.51 to 0.047], P=0.067) (**Figures 2B and 2C**).

Discussion

This randomized multicentre 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 post-transplantation in 80% of the grafted patients.[25] This may have been due to 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 HD patients, 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 (Figure S1), 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 favourably with the 43% reported in some pilot studies of fetal cell transplantation in HD.[14] This risk was eliminated by omitting the two 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 cohort of patients were unable to identify the key factors influencing transplant outcome.[14,26–30] The MIG-HD trial, with 45 grafted patients at six centres, 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 multicentre settings resulted in greater variability between centres 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 foetuses (from 1 to 2), presence of HLA antibodies, patients' gender, and duration of surgery; even if not proven statistically in these few individuals. It was unclear in the study by Paganini et al.[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. Whereas 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 alloimmunisation processes against the graft.[29,31] It might be the case that chronic inflammation due to alloimmunisation 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 to our pilot trial,[11] the use of older fetuses, the pooling of ganglionic eminences from several fetuses to increase graft volume, and reducing the inter-graft interval from one year to about two months, may have increased the risk of alloimmunisation. Here, 40% of patients developed HLA antibodies against the graft. In contrast, none of our patients from the pilot trial, with one-year intervals between transplants, had antibodies against the transplant five years after surgery (unpublished data). In two studies with short inter-graft 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] alloimmunisation appears to be a long process. However, functional impact of alloimmunization, reported in monkeys,[32] justifies better procedures to avoid alloimmunisation 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. Besides, in retrospect, the outcome measures lacked sensitivity (see[35]), which calls for new sensitive digitalised measures, as developed in the RepairHD program.

In summary, it could be concluded that grafts cannot restore the fronto-striatal 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 three patients across multiple outcomes analysed 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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References

1. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell. 1993;72:971–983.
2. Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol. 2014;10:204–216.
3. Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol. 2013;12:637–649.
4. Palfi S, Condé F, Riche D, et al. Fetal striatal allografts reverse cognitive deficits in a primate model of Huntington disease. Nat Med. 1998;4:963–966.
5. Dunnett SB, Nathwani F, Björklund A. The integration and function of striatal grafts. Prog Brain Res. 2000;127:345–380.
6. Zimmermann T, Remmers F, Lutz B, Leschik J. ESC-Derived BDNF-Overexpressing Neural Progenitors Differentially Promote Recovery in Huntington's Disease Models by Enhanced Striatal Differentiation. Stem Cell Reports. 2016;7:693–706.
7. Dunnett SB, Carter RJ, Watts C, et al. Striatal transplantation in a transgenic mouse model of Huntington's disease. Exp Neurol. 1998;154:31–40.
8. Reidling JC, Relaño-Ginés A, Holley SM, et al. Human Neural Stem Cell Transplantation Rescues Functional Deficits in R6/2 and Q140 Huntington's Disease Mice. Stem Cell Reports. 2018;10:58–72.
9. Al-Gharaibeh A, Culver R, Stewart AN, et al. Induced Pluripotent Stem Cell-Derived Neural Stem Cell Transplantations Reduced Behavioral Deficits and Ameliorated Neuropathological Changes in YAC128 Mouse Model of Huntington's Disease. Front Neurosci. 2017;11:628.
10. Bachoud-Lévi A-C. From open to large-scale randomized cell transplantation trials in Huntington's disease: Lessons from the multicentric intracerebral grafting in Huntington's disease trial (MIG-HD) and previous pilot studies. Prog Brain Res. 2017;230:227–261.
11. Bachoud-Lévi AC, Rémy P, Nguyen JP, et al. Motor and cognitive improvements in patients with Huntington's disease after neural transplantation. Lancet. 2000;356:1975–1979.
12. Reuter I, Tai YF, Pavese N, et al. Long-term clinical and positron emission tomography outcome of fetal striatal transplantation in Huntington's disease. J Neurol Neurosurg Psychiatry. 2008;79:948–951.
13. Bachoud-Lévi A-C, Gaura V, Brugières P, et al. Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery: a long-term follow-up study. Lancet Neurol. 2006;5:303–309.
14. Hauser RA, Furtado S, Cimino CR, et al. Bilateral human fetal striatal transplantation in Huntington's disease. Neurology. 2002;58:687–695.
15. Cicchetti F, Saporta S, Hauser RA, et al. Neural transplants in patients with Huntington's disease undergo disease-like neuronal degeneration. Proc Natl Acad Sci USA. 2009;106:12483–12488.
16. Cisbani G, Saint-Pierre M, Cicchetti F. Single-cell suspension methodology favors survival and vascularization of fetal striatal grafts in the YAC128 mouse model of Huntington's disease. Cell Transplant. 2014;23:1267–1278.
17. Freeman TB, Cicchetti F, Bachoud-Lévi AC, Dunnett SB. Technical factors that influence neural transplant safety in Huntington's disease. Exp Neurol. 2011;227:1–9.
18. Rosser AE, Bachoud-Lévi A-C. Clinical trials of neural transplantation in Huntington's disease. Prog Brain Res. 2012;200:345–371.
19. Keene CD, Chang RC, Leverenz JB, et al. A patient with Huntington's disease and long-surviving fetal neural transplants that developed mass lesions. Acta Neuropathol. 2009;117:329–338.
20. Gallina P, Paganini M, Lombardini L, et al. Human striatal neuroblasts develop and build a striatal-like structure into the brain of Huntington's disease patients after transplantation. Exp Neurol.

2010;222:30–41.
21. Spineli LM, Jenz E, Großhennig A, Koch A. Critical appraisal of arguments for the delayed-start design proposed as alternative to the parallel-group randomized clinical trial design in the field of rare disease. Orphanet J Rare Dis. 2017;12:140.
22. Cleret de Langavant L, Sudraud S, Verny C, et al. Longitudinal study of informed consent in innovative therapy research: experience and provisional recommendations from a multicenter trial of intracerebral grafting. PLoS ONE. 2015;10:e0128209.
23. Krystkowiak P, Gaura V, Labalette M, et al. Alloimmunisation to donor antigens and immune rejection following foetal neural grafts to the brain in patients with Huntington's disease. PLoS ONE. 2007;2:e166.
24. Bachoud-Lévi AC, Maison P, Bartolomeo P, et al. Retest effects and cognitive decline in longitudinal follow-up of patients with early HD. Neurology. 2001;56:1052–1058.
25. Gaura V, Bachoud-Lévi A-C, Ribeiro M-J, et al. Striatal neural grafting improves cortical metabolism in Huntington's disease patients. Brain. 2004;127:65–72.
26. Kopyov OV, Jacques S, Lieberman A, Duma CM, Eagle KS. Safety of intrastriatal neurotransplantation for Huntington's disease patients. Exp Neurol. 1998;149:97–108.
27. Bachoud-Lévi A, Bourdet C, Brugières P, et al. Safety and tolerability assessment of intrastriatal neural allografts in five patients with Huntington's disease. Exp Neurol. 2000;161:194–202.
28. Rosser AE, Barker RA, Harrower T, et al. Unilateral transplantation of human primary fetal tissue in four patients with Huntington's disease: NEST-UK safety report ISRCTN no 36485475. J Neurol Neurosurg Psychiatry. 2002;73:678–685.
29. Krebs SS, Trippel M, Prokop T, et al. Immune response after striatal engraftment of fetal neuronal cells in patients with Huntington's disease: Consequences for cerebral transplantation programs. Clinical and Experimental Neuroimmunology. 2011;2:25–32.
30. Paganini M, Biggeri A, Romoli AM, et al. Fetal striatal grafting slows motor and cognitive decline of Huntington's disease. J Neurol Neurosurg Psychiatry. 2014;85:974–981.
31. Porfirio B, Paganini M, Mazzanti B, et al. Donor-Specific Anti-HLA Antibodies in Huntington's Disease Recipients of Human Fetal Striatal Grafts. Cell Transplant. 2015;24:811–817.
32. Aron Badin R, Bugi A, Williams S, et al. MHC matching fails to prevent long-term rejection of iPSC-derived neurons in non-human primates. Nat Commun. 2019;10:4357.
33. Harrison DJ, Roberton VH, Vinh N-N, Brooks SP, Dunnett SB, Rosser AE. The Effect of Tissue Preparation and Donor Age on Striatal Graft Morphology in the Mouse. Cell Transplant. 2018;27:230–244.
34. Cisbani G, Freeman TB, Soulet D, et al. Striatal allografts in patients with Huntington's disease: impact of diminished astrocytes and vascularization on graft viability. Brain. 2013;136:433–443.
35. Schobel SA, Palermo G, Auinger P, et al. Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. Neurology. 2017;89:2495–2502.

Figure captions

Figure 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; MRI: magnetic resonance imaging; HD: Huntington's disease; TFC: Total Functional Capacity; MDRS: Mattis Dementia Rating Scale; UHDRS: Unified Huntington's Disease Rating Scale.

Figure 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 MIG-HD cohort through the piecewise linear mixed model over the pre- and post-graft time periods.

UHDRS: Unified Huntington's Disease Rating Scale.

Figure 3. SPM analysis at M32 comparing the treated patients and the control not yet treated groups at FDG scans

Regions in which changes in metabolism relative to the M12 baseline differed significantly between the treated group and control not yet treated group at M32 ($P<0.001$). These regions, overlaid on a T1-weighted brain MRI 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.

List of tables

Table 1. Demographic and baseline characteristics of patients

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