Neurodegenerative disease

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A neural stem-cell treatment for progressive multiple sclerosis

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A phase 1 trial using an allogeneic stem-cell-based therapy in people with progressive multiple sclerosis (MS) shows the feasibility and tolerability of the approach; rigorous evaluation of this and other regenerative strategies for MS is now urgently needed.

Advanced cell therapies — including those consisting of neural stem/progenitor cells (NPCs) — could potentially have a huge effect on the treatment of chronic disorders of the central nervous system (CNS), for which stopping, or even slowing, neurodegeneration and disease progression is a major unmet clinical need. Among these, progressive multiple sclerosis (PMS), encompassing primary and secondary forms of MS, involves an irreversible accumulation of disabilities caused by ongoing neurodegeneration in the context of diffuse (smoldering) CNS inflammation. There is a notable lack of well-characterized biological targets in PMS and hence a dearth of successful drugs. In looking to address these unmet needs, the multifactorial therapeutic benefits of stem-cell therapies — which provides neurotrophic support, immunomodulation and cell replacement[1] — are particularly compelling.

In this issue of *Nature Medicine*, Genchi et al.[2] begin to investigate, in the STEMS study, the innate multifunctionality and pro-regenerative potential of exogenous, tissue-specific advanced NPC therapeutics for people with PMS (Fig. 1). This single-center, dose-finding phase 1 clinical trial was designed to evaluate, for the first time, allogeneic human fetal-derived NPC (hfNPC) grafts in people with PMS. The rationale for using this strategy in PMS comes from preclinical research supporting the immunomodulatory potential of NPCs[1], as well as clinical trials for other neurodegenerative diseases, such as Parkinson's disease and amyotrophic lateral sclerosis, whereby allogeneic CNS progenitor/stem cells were transplanted to counteract neurodegeneration of the mesencephalic tissue[3] and to halt the progressive loss of motor neurons[4,5], respectively.

In the STEMS trial, the 12 participants each had 10–22 years of disease duration and severe disabilities and were ineligible for alternative disease-modifying therapies. Each patient received a single intrathecal injection — via a minimally invasive lumbar puncture — of hfNPCs derived from a single fetus. Four incremental cellular doses were evaluated, with three patients per treatment group.

First and foremost, STEMS met its primary endpoints of feasibility and tolerability, with no severe adverse reactions in the short,

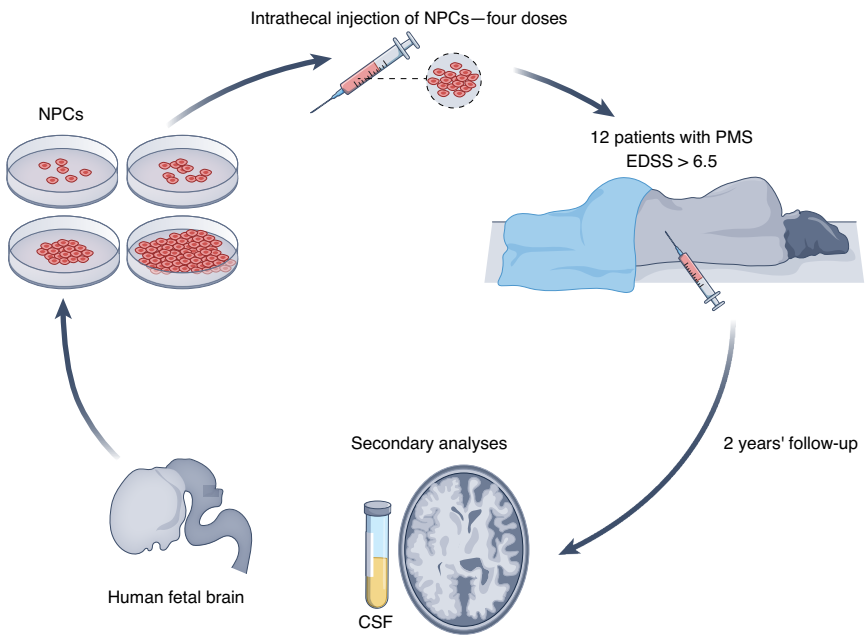

Fig. 1 | Schematics of the phase 1 STEMS clinical trial in people with progressive multiple sclerosis. Twelve people with PMS received a single intrathecal injection, via lumbar puncture, of hfNPCs derived from a single fetus. Four incremental cellular doses were evaluated, with three patients per treatment group. Primary outcomes included feasibility and tolerability. Secondary hypothesis-generating endpoints included the results of a battery of clinical, radiological and laboratory tests (clinicaltrials.gov identifier: NCT03269071). EDSS, expanded disability status scale.

medium or long term during the 2 years of follow-up. However, the results in regard to its secondary endpoints were partially positive, but difficult to interpret. Although all participants had advanced PMS and had severe disability, Genchi et al.[2] observed an unexpectedly high frequency of MRI-detectable disease activity: 6 of the 12 participants developed new T2 lesions, 50% of which were contrast enhancing, indicative of recent or currently active lesions. This finding is not easy to contextualize because of the lack of serial imaging (including post-contrast MRIs) before treatment initiation (or at baseline), which would allow researchers to establish patient-specific, annualized MRI disease activity. The immunosuppressive regimen used to prevent rejection of the allogenic graft (consisting of prednisone for 35 days and tacrolimus for the entire duration of the follow-up, in addition to antiviral and antibiotic treatments) also confounded the interpretation of some exploratory secondary endpoints related to the potential immunomodulatory effect of NPCs. Thus, caution is necessary in interpreting the changes in the expression levels of neurotrophic factors and anti-inflammatory cytokines in the CSF as evidence of neuroprotection or regeneration. Instead, cautious optimism arises from MRI brain and gray matter volume measurements showing lower rates of total brain and gray matter atrophy in the participants injected with the highest dose of hfNPCs, possibly suggesting a slowing of disease progression. However, this result is mostly subclinical, as all participants continued to worsen in terms of ambulatory ability and hand dexterity in the 2 years of follow-up, and the comprehensive battery of clinical and neurophysiological assessments did not provide any evidence of improvement.

The STEMS phase 1 trial demonstrates the feasibility and tolerability of hfNPC transplantation for people with PMS, but also raises a host of questions that future studies should aim to address — using study designs powered to detect differences in physiological and clinical outcomes, and incorporating a run-in phase that helps distinguish between active and non-active disease at baseline. On the basis of the current data from Genchi et al.[2], it is therefore still too early to say with any certainty whether an advanced CNS (stem) cell therapy with allogeneic hfNPCs is beneficial for people with PMS — but STEMS opens the door for further studies to better evaluate and build on this approach.

Phase 1 studies must be carefully interpreted to balance optimism with caution in any field, but particularly in this one. Indeed, the scientific community is constantly fighting against stem-cell 'tourism' and scam companies that are eager to supply unproven stem-cell therapies as a paid treatment to vulnerable and desperate people[1]. As a community, we must continue rigorous research, promoting independent phase 1 studies[6], and in this sense STEMS is a welcome first step forward. However, multicenter efficacy studies with increased statistical power, a proper gold standard of care control treatment (for example, disease-modifying treatments for active PMS) and more stringent patient selection and baseline assessments are now needed to definitively establish the usefulness of cell-based therapies in this setting.

We are surely living in an exciting time for regenerative medicine and cell therapies for CNS diseases. PMS is currently at the center of several stem-cell trials, in which autologous hematopoietic or mesenchymal stem/stromal cells have been administered with the aim of either resetting the immune system or exerting immunomodulatory and neuroprotective functions[7–9]. In addition, ongoing studies are leveraging cell reprogramming technology to generate autologous, clinical-grade neural cells or low-immunogenic heterologous cells to avoid the need for strong immunosuppression regimens[10,11]. Collectively, these studies will begin to address the challenges to the safe translation of stem-cell biology and medicine from bench to bedside.

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Competing interests

S.P. is founder, chief scientific officer and shareholder (>5%) of CITC Ltd and chair of the scientific advisory board at ReNeuron plc. The other authors have no conflicts to declare.