Autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis

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Title Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial.

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Summary

This was a single-group, phase 2 trial performed across three centres in Canada. The treatment protocol used in the trial differed from previous regimens by administering a graft depleted of immune cells using ex-vivo CD34 immunomagnetic graft selection. Inclusion criteria were patients aged 18–50 who were judged to have a high probability of significant disease progression over the subsequent 12 months based on natural history data.

Patients were followed up with standard clinical and MRI measures, initially every two months, increasing to every 6–12 months after three years. The primary outcome measure was multiple sclerosis (MS) activity-free survival at three years defined by lack of clinical relapse, new MRI lesions or sustained progression of Expanded Disability Severity Score (EDSS). Secondary outcomes were time to treatment failure (clinical relapse or progression), overall mortality, transplant-related mortality or morbidity, new MRI changes including atrophy, blood counts to monitor haemopoietic reconstitution as well as skin tests and serum antibody testing to monitor immunological reconstitution. The study also included some post hoc analysis including time to improvement in EDSS, relationships between baseline characteristics and changes in disease activity and social wellbeing.

Thirty-nine patients were screened, of whom 26 were eligible; 25 were enrolled and 24 completed the treatment. Twenty-one patients completed the 3-year core study and 13 were followed up in the extension study. Participants had a mean age of 34, 58% were female, 12 had relapsing remitting MS and 12 had secondary progressive MS. Mean disease duration was 6.1 years and median EDSS was 5.0 (range 3.0–6.0). Ten patients had previously been treated with one disease-modifying therapy (DMT), and 14 had been treated with two or more. The median duration of hospital admission was 29 days (range 22–170).

All patients had febrile neutropenia. Two patients had severe toxic effects which necessitated a change in the busulfan dose; one of these patients required ITU care and one died. Nine patients had late complications with viral infections and six had secondary autoimmune events. Two patients elected to receive experimental treatments outside of the trial and were therefore censored from the study after 14 and 23 months. Both of these patients experienced gradual increase in disability but neither had clinical or radiological evidence of focal inflammatory activity.

The primary outcome of MS activity-free survival was achieved in 16/23 patients (69.6%); failure to reach this end point was fully accounted for by seven patients who experienced sustained progression of disability. There were no clinical relapses or new MRI activity in the surviving 23 patients in the core study or extension period comprising 179 patient-years of follow up and including 327 MRI scans over a median of 6.7 years of follow up.

The authors comment that the baseline characteristics, which included disease subtype, did not predict EDSS progression. Rates of atrophy increased in the first six months but stabilised after two years to a rate which is comparable to the general population. There was an improvement in EDSS of between 0.5 and 3.0 points over the entire time period in 40% of patients.

The authors claim that this is the first treatment for MS to fully halt all detectable CNS inflammatory activity for a long period in the absence of disease-modifying drugs. In addition, brain atrophy slowed to a sustained lower rate

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associated with normal ageing. Although 7/24 patients continued to progress, the authors argue that this rate is at the lower end of previous studies of autologous haematopoietic stem cell transplantation (AHSCT) in MS and that this supports the approach of treating early aggressive MS with more potent therapies.

Opinion

MS is the most common cause of neurological disability in young adults. It typically starts with a relapsing remitting phase that transforms into a secondary progressive phase in the majority of cases. DMTs are licensed for treatment of active relapsing remitting MS but their effectiveness in treating progression has been disappointing.[1]

Current protocols for DMTs for MS in the UK encourage an escalation approach to therapy with first and second line DMTs;[2] first line agents are less efficacious but are safer. There are calls for a change to an 'induction' strategy of using more aggressive therapies in the early active stages of the disease before permanent damage to the CNS is established in order to delay or halt future progression.[3]

AHSCT has been studied for 20 years[4] and is regarded as an aggressive treatment option. Its role is not well established within MS treatment protocols due to higher mortality rates, poor tolerability of the procedure and practical difficulties in undertaking and recruiting to high quality randomised controlled studies comparable to phase 3 drug trials.

The treatment protocol employed in this study differed from previous studies in the use of a higher-dose regimen for immunoablation and depletion of mature lymphocytes. The aim of this more aggressive approach was to reset immunological memory and the authors provided evidence for this with reduced or eliminated immune responses to candida, tetanus, BCG and MMR which are not described with established MS therapies.

The primary outcome measure demonstrated impressive efficacy in comparison to previous AHSCT trials in MS, which found decreases in relapse rates of 80% after four years, and 78.4% of patients free from clinical relapse, sustained progression and new MRI lesions after three years.[5,6] The authors emphasise that this absolute response was sustained over a median 6.7 years of follow-up.

This study was non-randomised and non-blinded and the reliability of the findings is not comparable to a phase 3 trial. The numbers are small and confidence intervals regarding efficacy and safety risks are consequently wide. Outcomes from previous trials of immunomodulatory treatments including AHSCT are much poorer or absent in progressive MS.[1,7,8] It is difficult to conclude that this new regimen is profoundly different based on such small numbers that carry a significant chance of a type 2 statistical error. The small numbers also prevent any stratification of the data to generate hypotheses concerning which subgroups might benefit from this higher risk approach. The lack of blinding and a placebo group is likely to exaggerate the apparent clinical benefits due to the natural history of MS, a placebo effect and regression to the mean.

However, the study includes an objective measure in the form of MRI findings and the outcomes compare favourably with a study of alemtuzumab which is currently considered to be the most effective DMT. During a 6-year study of alemtuzumab therapy, 57% of patients were free of clinical relapses, new MRI activity or sustained progression of disability and 36% were re-treated due to evidence of clinical relapse or new MRI lesion.[9]

The paper makes a distinction between early CNS inflammatory activity and later progression. The authors argue that stopping future progression requires targeting patients at a time when they still have active CNS inflammation. This is an important distinction when considering the long term effects of immunomodulating therapies since the link between these two processes is complex and is not fully understood. Several sources of evidence demonstrate an association between early relapses and later progression.[10–13] However, it is not yet established that early focal inflammation is the root cause of progression as independent cohorts have found age to be a risk factor for disease progression that is independent of relapses.[14–16] In view of this, it should not be assumed that halting features of inflammation will necessarily prevent long term progression and the data on atrophy and progression in this paper merit further examination.

The gradual progression of disability seen in 30% of patients with a baseline EDSS of 3.0–6.0, over a median 6.7-year follow up compares favourably with natural history studies which found 80% of patients progressed from EDSS 3.0 to 6.0 within 12 years.[17] However, the numbers are small and the cohort was selected to include atypical patients with a poor prognosis. Natural history data do not apply to this group and results from this unusual group may not apply to typical MS. The sustained low rates of atrophy are promising and hint at a delayed effect on progressive MS but this cannot be confirmed by the current trial.

The landscape of DMTs for MS has changed significantly since the trial began recruiting in 2000; there are now more convenient oral treatments and more effective antibody-based therapies available. These treatments are not associated with the higher mortality and morbidity rates seen with AHSCT. They have been studied in larger trials that have produced more reliable estimates of risks and benefits and with the current level of evidence, it seems likely that AHSCT will remain an option reserved for atypical aggressive cases of MS that are resistant to other treatments.

References

1 Ontaneda D, Fox RJ, Chataway J. Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives. *Lancet Neurol* 2015; 14: 208–23.
2 NHS England. *Clinical commissioning policy: Disease modifying therapies for patients with Multiple Sclerosis*. May 2014. NHS England/D04/P/b.
3 MS Society. Time to Act – a consensus on early treatment. 2015.
4 Mancardi G, Saccardi R. Autologous haematopoietic stem-cell transplantation in multiple sclerosis. *Lancet Neurol* 2008; 7: 626–36.
5 Burt RK, Balabanov R, Han X et al. Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis. *JAMA* 2015; 313: 275–84.
6 Nash RA, Hutton GJ, Racke MK et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for relapsing-remitting multiple sclerosis (HALT-MS): a 3-year interim report. *JAMA Neurol* 2015; 72: 159–69.
7 Coles AJ, Wing MG, Molyneux P et al. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. *Ann Neurol* 1999; 46: 296–304.
8 Krasulová E, Trneny M, Kozák T et al. High-dose immunoablation with autologous haematopoietic stem cell transplantation in aggressive multiple sclerosis: a single centre 10-year experience. *Mult Scler* 2010; 16: 685–93.
9 Coles AJ, Boyko AN, Cohen JA et al. *Alemtuzumab provides durable improvements in clinical outcomes in treatment-naive patients with active relapsing-remitting multiple sclerosis over 6 years in the absence of continuous treatment (CARE-MS I)*. London: ECTRIMS; 2016.
10 Confavreux C, Vukusic S, Moreau T et al. Relapses and progression of disability in multiple sclerosis. *N Engl J Med* 2000; 343: 1430–8.
11 Fisher E, Rudick RA, Simon JH et al. Eight-year follow-up study of brain atrophy in patients with MS. *Neurology* 2002; 59: 1412–20.
12 Chard DT, Brex PA, Ciccarelli O et al. The longitudinal relation between brain lesion load and atrophy in multiple sclerosis: a 14 year follow up study. *J Neurol Neurosurg Psychiatry* 2003; 74: 1551–4.
13 Scalfari A, Neuhaus A, Degenhardt A et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain* 2010; 133(Pt 7): 1914–29.
14 Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. *Brain* 2006; 129(Pt 3): 595–605.
15 Leray E, Yaouanq J, Le Page E et al. Evidence for a two-stage disability progression in multiple sclerosis. *Brain* 2010; 133(Pt 7): 1900–13.
16 Scalfari A, Neuhaus A, Daumer M et al. Age and disability accumulation in multiple sclerosis. *Neurology* 2011; 77: 1246–52.
17 Pittock SJ, Mayr WT, McClelland RL et al. Disability profile of MS did not change over 10 years in a population-based prevalence cohort. *Neurology* 2004; 62: 601–6.