

potential must evolve to become less toxic so that subsequent lines of therapy remain feasible.

The second issue is even more challenging to address. Phase 3 trials that target overall survival remain the gold standard but face feasibility issues or irrelevance if they take too long. Trialists should take heart that Hermine and colleagues' study<sup>1</sup> started in 2004, yet it yielded results that are as relevant today as when the study was first conceived. Treatments that improve response depth or duration but not survival might have value that is not immediately apparent, but results must be assessed in the context of toxicity and effect on subsequent therapies.

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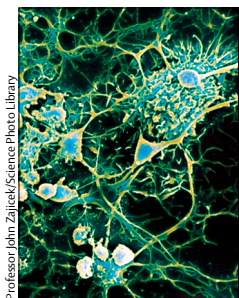
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I report consulting fees from Gilead and Novartis for work unrelated to mantle cell lymphoma, and from Acerta, Celgene, and Janssen for work related to mantle cell lymphoma.

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## W Haemopoietic stem-cell transplantation for multiple sclerosis: what next?



Professor John Zallack/Science Photo Library

With approximately 2 million people affected worldwide, multiple sclerosis is among the most common chronic inflammatory diseases of the CNS, and despite major therapeutic advances in recent years, the disease is still insufficiently controlled in many patients.<sup>1</sup> It is thought to be caused by autoimmunity. Therefore, resetting the adaptive immune system by eliminating aberrant self-reactive immune cells and inducing a more tolerant immunity is a potential treatment. Indeed, immunoablation and subsequent autologous haemopoietic stem-cell transplantation (aHSCT) have been investigated in patients with treatment-refractory multiple sclerosis. However, not surprisingly in view of small

sample sizes, different cohort characteristics, varying protocols for aHSCT, and toxic effects of treatment, results have varied.<sup>2</sup> Mortality is roughly 5% and many patients continue to have clinical or radiological signs of disease activity.<sup>3</sup> Consequently, aHSCT is considered a last resort for patients with highly active and treatment-refractory disease who have a poor prognosis. This perception might now be challenged by new data.

In *The Lancet*,<sup>4</sup> Harold Atkins and colleagues present results from a multicentre single-arm trial of aHSCT in 24 patients with aggressive treatment-refractory multiple sclerosis. They showed that immunoablation with busulfan, cyclophosphamide, and rabbit

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anti-thymocyte globulin, followed by transplantation of autologous CD34-selected haemopoietic stem-cell grafts, completely arrested both the occurrence of new relapses and the development of new lesions on MRI for a mean follow-up period of 7.5 years (179 patient-years for 24 patients) in the absence of disease-modifying drugs. Before aHSCT, all patients had progressive loss of neurological function, whereas 70% remained clinically stable after aHSCT with a median follow-up of 6.7 years. Disability progression in the remaining 30% was rather mild. Neurological function improved in roughly 40% of patients, which is remarkable given the high baseline disability status. Furthermore, the rate of MRI-determined brain atrophy declined to that expected for healthy people.

Given that before aHSCT participants had aggressive disease with continuing relapses, rapid disability progression, and high MRI activity despite treatment with disease-modifying drugs, these results are impressive and seem to outbalance any other available treatment for multiple sclerosis. This trial is the first to show complete suppression of any inflammatory disease activity in every patient for a long period. Although not directly comparable, even treatment with alemtuzumab, an immune-cell-depleting monoclonal antibody and considered the most powerful drug for multiple sclerosis, achieved complete control of disease activity in only 32% of patients in a similar cohort.<sup>5</sup>

The anti-inflammatory effect shown by Atkins and colleagues further distinguishes their study from three other aHSCT trials,<sup>6–8</sup> which had similar proportions (68–80%) of patients with complete disease control (no relapses, no disease progression, no MRI activity) over 3–5 years of follow-up. In these studies, 13–20% of patients still had relapses, which suggests incomplete suppression of inflammation. Different aHSCT protocols and particularly the ex-vivo selection of CD34 cells might explain the more powerful anti-inflammatory effect reported by Atkins and colleagues. The trial, however, was not controlled with a placebo or active comparator group, which is probably the most important limitation of the study.

aHSCT has a poor safety profile, especially with regards to treatment-related mortality. In the study by Atkins and colleagues, one patient died from massive

hepatic necrosis and klebsiella sepsis 2 months after aHSCT. This mortality of roughly 4% accords with previous data on aHSCT-related mortality in patients with multiple sclerosis.<sup>2,3</sup> Although some data suggest that mortality can be decreased to 1–2% in experienced centres,<sup>2</sup> mortality is nonetheless substantially higher than for any other approved disease-modifying drug.

So, will this study change our approach to treatment of multiple sclerosis? Probably not in the short term, mainly because the mortality rate will still be considered unacceptably high. Over the longer term, however, and in view of the increasing popularity of using early aggressive treatment, there may be support for considering aHSCT less as a rescue therapy and more as a general treatment option, provided the different protocols are harmonised and optimised, the tolerability and safety profile can be further improved, and prognostic markers become available to identify patients at risk of poor prognosis in whom a potentially more hazardous treatment might be justified.

For now, two points seem important. First, aHSCT should remain restricted to specialised centres experienced both in multiple sclerosis and haemopoietic stem-cell treatment, and all efforts taken to prevent stem-cell tourism. Second, integrating experiences and lessons learned from the different aHSCT studies should continue and be expedited to assess the real value of aHSCT for the treatment of multiple sclerosis.<sup>9</sup>

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## England’s Teenage Pregnancy Strategy: a hard-won success

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Teenage pregnancy is considered a key indicator of adolescent health for good reason.<sup>1</sup> The associations between teenage births and mortality, morbidity, and social and economic hardship for the mother and child are well established. Research over many decades has provided us with a good understanding of the underlying factors for the complex issue of teenage pregnancy and reasonable evidence for what strategies work to limit it. In *The Lancet*, Kaye Wellings and colleagues<sup>2</sup> present the impact of the UK Teenage Pregnancy Strategy on rates of teenage abortions and births in England over the 13 years after its introduction in 2000.<sup>3</sup>

The Teenage Pregnancy Strategy was a complex, intersectoral, and multicomponent intervention, informed by available evidence on likely effective strategies to reduce pregnancies, from inception throughout its funding period. There were three main components of the strategy. The first element was a whole-government approach to administration, headed by a cross-departmental ministerial task force (spanning the departments of health, education, and employment), monitored by an independent national advisory group

and implemented by funded regional and local service coordinators and partnership boards. The second element was improved prevention efforts, including: high quality education about sex and relationships in schools; better access to effective contraception; enhanced efforts targeting the most at-risk groups, and young males; a media campaign with separate components for young people and parents; and a print and broadcast media campaign. The third element was better support for pregnant teenagers and teenage parents to ensure completion of education and access to secure housing with in-home support for mothers and their children. At the mid-course review in 2005, the UK’s national conception rate had dropped 11% for those younger than 18 years and 15% for those younger than 16 years, but with variability, including reductions as substantial as 43% in one local authority.<sup>4</sup> From this point, a more intensive approach to lower-performing authorities was adopted.<sup>5</sup>

In the study by Wellings and colleagues,<sup>2</sup> investigators combined routinely collected area-level data on abortions and births, deprivation, and Local Implementation Grant expenditures with individual-level risk factor information from the three waves of the National Surveys of Sexual Attitudes and Lifestyle (Natsal) to describe changes in conception, abortions, and maternities in individuals younger than 18 years in England from 2000 to 2013. The maternity rate of individuals younger than 18 years in England has decreased slowly but steadily from its peak in 1996–98, but much more rapidly from 2007 to 2013, along with a decline in the abortion rate, halving the conception rate overall. The most substantial reductions were in the most deprived areas, where rates were originally highest. Participation in work, education, or training by young women who became mothers before age 18 years doubled over the period of the Teenage Pregnancy Strategy. The authors also estimated an absolute decrease in conception rate of between 8.2 conceptions



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