



Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Autologous haematopoietic stem cell transplantation for previously treated, relapsing-remitting multiple sclerosis
Topic exploration report number:	TER107

Introduction and aims

Multiple sclerosis is an autoimmune disease where the immune system 'self-targets' and attacks the myelin sheath in the brain and spinal cord. Symptoms include pain, chronic fatigue, muscle stiffness and spasms, difficulty walking or keeping balance, incontinence, and visual or cognitive difficulties. People with relapsing-remitting multiple sclerosis will have episodes of remission (mild or no symptoms) and periods of new or worsening symptoms. People with relapsing-remitting multiple sclerosis can progress to secondary progressive multiple sclerosis. This is a more persistent type of multiple sclerosis (no remission) with increased worsening of the condition.

Autologous haematopoietic stem cell transplantation is a procedure where haematopoietic stem cells (stem cells that can develop into all types of blood cells) are harvested from the peripheral blood or bone marrow of the patient. The patient is then treated with chemotherapy and immunosuppressive therapy to destroy the self-reactive immune cells. The harvested stem cells are used to repopulate the patient's immune system.

Health Technology Wales researchers searched for evidence on autologous haematopoietic stem cell transplantation for previously treated, relapsing-remitting multiple sclerosis.

Summary of evidence

The British Society of Blood and Marrow Transplantation (BSBMT) recommends the clinical adoption of autologous haematopoietic stem cell transplantation in severe, resistant multiple sclerosis. The procedure is commissioned at two specialised centres in NHS England; the NHS England Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies recommends that it is made more equitably available for people with relapsing multiple sclerosis who have failed the currently available therapies.

This report identified several sources of evidence on autologous stem cell transplantation for people with multiple sclerosis - the subtype of multiple sclerosis was not always clear or defined.

Health technology assessments

The National Institute for Health and Care Excellence (NICE) explored “Autologous haematopoietic stem cell transplantation for treating relapsing-remitting multiple sclerosis” in 2017. Stakeholders considered the topic was appropriate for consultation because routine commissioning may make it easier for patients to access the procedure, which is currently only available in Sheffield and London. Following scoping and consultation, NICE determined that an appraisal of the topic would not be appropriate; this was because none of the chemotherapy drugs used in the most relevant ongoing trial (NCT00273364) are licensed for stem cell transplantation or multiple sclerosis. NICE also concluded that a technology appraisal was unlikely to add value, as a clinical commissioning policy already exists in NHS England.

Systematic review and meta-analysis

One systematic review was identified (Li et al., 2016) that aimed to evaluate the effects of haematopoietic stem cell transplantation for adults with multiple sclerosis. The analysis included 8 single arm studies; the evidence suggested that haematopoietic stem cell transplantation for people with MS reduces the EDSS score at 12 months (or longest follow-up time more than 10 months). The authors reported high heterogeneity between the studies, although did not believe this to be a contributing factor to the analysis. Quality was not assessed due to the limited nature of included studies.

Primary studies

Multiple primary studies were identified that reported haematopoietic stem cell transplantation for people with multiple sclerosis, several of which were published following the systematic review. Study design varied and included phase II trials, retrospective cohort studies and one randomised comparative trial. Overall, the studies report improved clinical outcomes for people with multiple sclerosis who receive autologous stem cell transplants.

A recently published randomised comparative study (Burt et al., 2019) reports preliminary data from the main ongoing study that is referenced in NICE’s scoping report (NCT00273364). It reports improved EDSS scores and prolonged time to disease progression in the arm receiving haematopoietic stem cell transplants.

Ongoing studies

Three ongoing studies were identified. The aforementioned NCT00273364 is the only study with centres located in the UK. The remaining two ongoing studies are set in USA (NCT03133403) and other European countries (Denmark, Netherlands, Norway, Sweden; NCT03477500).

Areas of uncertainty

The population for this exploration is people with previously treated, relapsing-remitting multiple sclerosis. There may be other types of multiple sclerosis that could be suitable for autologous haematopoietic stem cell transplantation.

It is unclear whether this procedure would be suitable for people under the age of 18 years, or whether evaluation of this technology should be limited to an adult population.

Should this topic proceed to full appraisal, further scoping is required to establish the most appropriate place for autologous haematopoietic stem cell transplantation in the treatment pathway, for example whether this procedure would only be considered as a 'last line' option, once all other alternative treatments have been exhausted.

We did not identify any economic evidence of relevance.

Conclusions

We identified multiple sources of evidence on autologous haematopoietic for people with multiple sclerosis. Overall, the evidence showed potential benefits for the procedure; however, further assessment would be needed to confirm the appropriateness of the evidence, and whether or not it is of sufficient quality.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any results on AHST for people with multiple sclerosis.
Health Technology Assessment Group	We did not identify any results on AHST for people with multiple sclerosis.
Health Information and Quality Authority	We did not identify any results on AHST for people with multiple sclerosis.
UK guidelines and guidance	
SIGN	We did not identify any results on AHST for people with multiple sclerosis.
NICE	<p>Autologous haematopoietic stem cell transplantation for treating multiple sclerosis (ID1111)</p> <p>Batch 62 block scoping report</p> <p>March 2017 - August 2018</p> <p>Following scoping and consultation NICE deemed that an appraisal of this topic was not appropriate.</p>
Secondary literature and economic evaluations	
ECRI	We did not identify any results on AHST for people with multiple sclerosis.
EUnetHTA	<p>We did not identify any evidence reports or HTA reports on AHST for people with multiple sclerosis.</p> <p>We did identify relevant 'Technology News':</p> <p>Five-year Study Helps Define Stem Cell Transplantation's Promise, Risk for Treating Multiple Sclerosis</p> <p>Published 03/03/2017</p>
Cochrane library	<p>We did not identify any secondary evidence on AHST for people with multiple sclerosis.</p> <p>We identified a relevant protocol for a Cochrane review: Stem cell therapy for multiple sclerosis. June 2018.</p>
Medline	<p>Li C, Feng J, Chen S, et al. (2016). Efficacy of hematopoietic stem cell for multiple sclerosis, an evidence based meta-analysis. Cellular & Molecular Biology. 62(4): 48-52.</p> <p>http://ovidsp.ovid.com/athens/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med12&AN=27188734</p>
Primary studies	
Cochrane library	<p>Burt RK, Balabanov R, Burman J, et al. (2019). Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis: a Randomized Clinical Trial. JAMA. 321(2): 165-74. doi: 10.1001/jama.2018.18743. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01792475/full</p> <p>Sormani MP, Muraro PA, Saccardi R, et al. (2017). NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. Multiple sclerosis (Houndmills,</p>

Basingstoke, England). 23(2): 201-4. doi: 10.1177/1352458516645670.

<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01340190/full>

Nash RA, Hutton GJ, Racke MK, et al. (2017). High-dose immunosuppressive therapy and autologous HCT for relapsing-remitting MS. *Neurology*. 88(9): 842-52. doi: 10.1212/WNL.0000000000003660.

<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01339900/full>

Tolf A, Granberg T, Larsson EM, et al. (2017). Corpus callosum atrophy in MS is halted by autologous haematopoietic stem cell transplantation. *Multiple sclerosis journal*. 23(3): 1006-7. doi: 10.1177/1352458517733228. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01427967/full> (Conference abstract)

Mancardi GL. (2017). Autologous haematopoietic stem cell transplantation in severe forms of multiple sclerosis. *European journal of clinical investigation*. Conference: 51st annual scientific meeting of the european society for clinical investigation. Italy. 47: 59.

<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01376592/full> (Conference abstract)

Boffa G, Curro D, Capobianco M, et al. (2017). Sustained disease remission in aggressive multiple sclerosis after autologous haematopoietic stem cell transplantation. *European journal of neurology*. Conference: 3rd congress of the european academy of neurology. Netherlands. 24: 770. doi: 10.1111/ene.13372.

<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01398419/full> (Conference abstract)

Atkins HL, Freedman MS. (2017). Five Questions Answered: a Review of Autologous Hematopoietic Stem Cell Transplantation for the Treatment of Multiple Sclerosis. *Neurotherapeutics*. 1-6. doi: 10.1007/s13311-017-0564-5. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01404747/full> (Review)

Atkins HL, Bowman M, Allan D, et al. (2016). Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. *Lancet (london, england)*. 388(10044): 576-85. doi: 10.1016/S0140-6736(16)30169-6.

<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01179430/full>

Mancardi GL, Sormani MP, Gualandi F, et al. (2015). Autologous hematopoietic stem cell transplantation in multiple sclerosis. *Neurology*. 84(10): 981-8. doi: 10.1212/WNL.0000000000001329.

<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01069436/full>

Clay J, Kelsey P, Bell S, et al. (2015). Autologous haematopoietic stem cell transplantation in aggressive multiple sclerosis: a UK cohort from two centres. *Bone marrow transplantation*. 50: S61-. doi: 10.1038/bmt.2015.27.

<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01778607/full>

	<p>Burman J, Iacobaeus E, Svenningsson A, et al. (2014). Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience. <i>Journal of neurology, neurosurgery and psychiatry</i>. doi: 10.1136/jnnp-2013-307207. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01771281/full</p> <p>Novik AA, Kuznetsov AN, Melnichenko VY, et al. (2010). Reduced intensity conditioning regimen of autologous hematopoietic stem cell transplantation (+/-) mitoxantrone consolidation in multiple sclerosis. <i>Blood</i>. 116(21). https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00784087/full (Conference abstract)</p>
Medline	<p>Moore JJ, Massey JC, Ford CD, et al. (2019). Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis. <i>Journal of Neurology, Neurosurgery & Psychiatry</i>. 90(5): 514-21. doi: https://dx.doi.org/10.1136/jnnp-2018-319446</p> <p>Mariottini A, Innocenti C, Forci B, et al. (2019). Safety and efficacy of autologous hematopoietic stem-cell transplantation following natalizumab discontinuation in aggressive multiple sclerosis. <i>European Journal of Neurology</i>. 26(4): 624-30. doi: https://dx.doi.org/10.1111/ene.13866.</p> <p>Guillaume-Jugnot P, Badoglio M, Labopin M, et al. (2019). Autologous haematopoietic stem cell transplantation (AH SCT) in autoimmune disease adult patients in France: analysis of the long-term outcome from the French Society for Bone Marrow Transplantation and Cellular Therapy (SFGM-TC). <i>Clinical Rheumatology</i>. 38(5): 1501-11. doi: https://dx.doi.org/10.1007/s10067-019-04435-2.</p> <p>Lee H, Nakamura K, Narayanan S, et al. (2018). Impact of immunoablation and autologous hematopoietic stem cell transplantation on gray and white matter atrophy in multiple sclerosis. <i>Multiple Sclerosis</i>. 24(8): 1055-66. doi: https://dx.doi.org/10.1177/1352458517715811</p> <p>Bose G, Atkins HL, Bowman M, et al. (2018). Autologous hematopoietic stem cell transplantation improves fatigue in multiple sclerosis. <i>Multiple Sclerosis</i>. 1352458518802544. doi: https://dx.doi.org/10.1177/1352458518802544</p> <p>Kyrcz-Krzemien S, Helbig G, Torba K, et al. (2016). Safety and efficacy of hematopoietic stem cells mobilization in patients with multiple sclerosis. <i>Hematology</i>. 21(1): 42-5. doi: https://dx.doi.org/10.1179/1607845415Y.0000000049</p>
Ongoing primary or secondary research	
PROSPERO database	We did not identify any results on AH SCT for people with multiple sclerosis.
Clinicaltrials.gov	<p>NCT00273364. Hematopoietic Stem Cell Therapy for Patients With Inflammatory Multiple Sclerosis Failing Alternate Approved Therapy: A Randomized Study. Estimated study completion Sep 2024.</p> <p>NCT03477500. Randomized Autologous Hematopoietic Stem Cell Transplantation Versus Alemtuzumab for Patients With Relapsing Remitting Multiple Sclerosis. Estimated study completion Mar 2024.</p> <p>NCT03133403. Hematopoietic Stem Cell Therapy for Patients With Inflammatory Multiple Sclerosis Failing Alternate Approved Therapy: A Randomized Study. Estimated study completion Sep 2024.</p>

Other	
Search for NHS commissioning, stem cell, MS	<p>Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies. NHS England Reference: 170079ALG. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf</p> <p>Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation https://www.england.nhs.uk/wp-content/uploads/2013/04/b04-p-a.pdf</p> <p>Horizon Scanning Research & Intelligence Centre. Autologous haematopoietic stem cell transplantation for relapsing remitting multiple sclerosis - second line. http://www.io.nihr.ac.uk/wp-content/uploads/migrated/AHSCR-June16.pdf</p> <p>BRITISH SOCIETY OF BLOOD AND MARROW TRANSPLANTATION. Indications table. http://www.bsbmt.org/indications-table/</p>

Date of search:	June 2019
Concepts used:	stem cell, multiple sclerosis