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Autologous haematopoietic cell transplantation in multiple sclerosis

Abstract

Introduction: Autologous haematopoietic cell transplantation (AHCT) is an evolving treatment avenue in multiple sclerosis (MS), which may be highly effective in controlling disease activity and improving disability. However, AHCT is associated with intrinsic toxicities and risks compared with conventional therapies. With growing experience in patient selection and treatment delivery, AHCT is increasingly considered an option in patients with aggressive disease responding poorly to disease modifying therapy.

Areas Covered: The introduction and development of AHCT as a treatment for MS over the last 20 years, potential mechanisms of action, patient selection, and future trends for this treatment approach.

Expert Opinion: AHCT represents an extremely efficacious treatment for inflammatory phase MS. Currently published data suggest that its use is associated with significant reduction in disease activity and marked improvement in disability when used in patients with highly active relapsing remitting disease. Its long term safety and efficacy have not been fully evaluated but as increasing clinical trial data are published, its use is likely to grow. Further randomised controlled studies are needed to compare AHCT with standard disease modifying therapies and to optimise transplant regimens. Mechanistic studies may provide potential markers for response and a better understanding of disease pathogenesis.

Abbreviations

rATG   Rabbit Anti-Thymocyte Globulin

AHCT   Autologous Hematopoietic Cell Transplantation

BEAM   BCNU, Ara-C, etoposide and melphalan

BuCy   Busulfan, cyclophosphamide, and rabbit ATG

CNS   Central Nervous System

EBV-PTLD   Epstein-Barr Virus related post-transplant lymphoproliferative disorder

EBMT   European Society for Blood and Marrow Transplantation

EDSS   Expanded Disability Status Scale

G-CSF   Granulocyte-colony stimulating factor

MSC   Mesenchymal stem (or stromal) cell

MRI   Magnetic resonance imaging

MS   Multiple sclerosis

NEDA   No evidence of disease activity

PPMS   Primary progressive multiple sclerosis

RRMS   Relapsing remitting multiple sclerosis

SPMS   Secondary progressive multiple sclerosis

TBI   Total body irradiation

TRM   Treatment related mortality

1.1 Introduction

Multiple Sclerosis (MS) is an autoimmune disease that affects the central nervous system (CNS). It has a prevalence of 203.4 per 100 000 population in the UK [1]. Its incidence increases with increasing latitude, it is more common in women and it usually presents between the ages of 20 and 40 [2]. The classical pathological hallmarks are plaques of demyelination associated with inflammation and axonal transection, which develop anywhere within the CNS and the optic nerves. The disease has a very variable course making its symptoms and signs very heterogeneous.

The clinical course of MS was traditionally categorised into three main subtypes: primary progressive (PPMS) where patients develop gradually worsening neurological disability with no relapses, relapsing remitting (RRMS), where patients develop relapses with complete or partial recovery followed by periods of stability, and secondary progressive (SPMS) where patients start with a relapsing and remitting course which culminates in periods of progressive accumulation of disability with or without superimposed relapses.

More recently the clinical course of MS has been redefined based on disease activity and progression into a relapsing (which accounts for the RRMS) and progressive (which accounts for both PPMS and SPMS) phases [3] see figure 1.

The two clinical courses of the disease probably have different pathogenic mechanisms. RRMS symptoms are driven by an inflammatory process within the nervous system, whereas in PPMS and SPMS inflammation is less evident and axonal degeneration is thought to be the main driver of disability progression. This is evidenced by the fact that both PPMS and SPMS do not readily respond to the same immunosuppressive treatments as RRMS.

The physical impact of MS on affected patients results in disability which is traditionally measured using the Kurtzke Expanded Disability Status Scale or (EDSS) [4] (Table 1). This

is an ordinal scale which combines the findings of the neurological examination and patients' ambulation in a single score between 0 (normal) and 10 (dead due to MS). Along with annualized relapse rate and MRI disease activity, the EDSS is frequently used in clinical trials as a primary outcome measure. More recently, the concept of 'no evidence of disease activity (NEDA), characterised by the absence of clinical relapses, disability progression and MRI disease activity, has been suggested as an ultimate goal of treatment response.

Over the last 30 years, the main focus of therapeutic interventions in RRMS has been to modulate the immune system to stop the inflammatory process which causes the neuronal damage and subsequent disability. Currently available disease modifying therapies used in RRMS do, to varying degrees, reduce relapse rate and slow down the accumulation of disability, but they cannot halt its progression. There are currently no licensed treatments for the progressive forms of MS.

Based on animal models and serendipitous case reports, Autologous Hematopoietic Cell Transplantation (AHCT) has been a used as treatment for MS for over two decades. The treatment was used initially in patients with advanced progressive disease as a rescue therapy to try and halt disease progression. Limited efficacy was seen in this group of patients. More recently its use in patients with active RRMS has been associated with prolonged clinical and MRI responses, and, in some cases, an improvement in disability to a degree rarely seen with other treatments.

In this paper we will review the development AHCT as a treatment for MS, its mechanism of action, patients' selection, treatment regimens and their safety profiles. We will compare the efficacy of AHCT to standard disease modifying therapies used mainly in RRMS, as this is where the more up to date research is focused, and comments of the future of this testament within the therapeutic algorithm.

2.1 History of AHCT in MS

The rationale for using AHCT as a treatment MS came from the observation that remission of co-existing severe autoimmune diseases occurred when using AHCT for the treatment of haematological malignancies [5]. As well as achieving remission, AHCT was shown to improve the symptoms of MS when used to treat haematological malignancies in patients with MS [6]. Rodent models of MS, specifically Experimental Autoimmune Encephalomyelitis, also showed that the disease could be arrested with AHCT [7], although caution in interpreting these results was needed due to the limitations of animal models. The first reported patients with MS treated with AHCT were in Thessaloniki in 1995 [8]. Since then, the European Society for Blood and Marrow Transplantation (EBMT) registry has over 800 patients for MS (personal communication, EBMT Registry) [9].

Initially, the majority of the patients treated had secondary progressive MS [8;10]. This early experience showed that, although AHCT seemed to reduce gadolinium enhancement in brain MRI imaging, it did not prevent progression of the disease or improve patients' outcome [11;12]. With increasing experience, patients with RRMS were increasingly treated and noted to have a more favourable response, with reduction in clinical relapses, MRI disease activity and disability progression. In some patients an improvement in the EDSS score was also noted [13].

In addition, increasing experience has led to significant modification of the conditioning regimens. Initially, several regimens included the use of total body irradiation (TBI) [10] and Busulfan [11;14;15]**.** These regimens were associated with high morbidity and mortality [14;16]. TBI was postulated to accelerate progression of disability in patients with secondary and primary progressive forms of MS as a result of the radiation induced axonal damage [17]. A meta-analysis of AHCT regimens classed as high intensity (containing TBI and Busulfan)

or medium intensity (mainly containing BEAM [BCNU, Ara-C, etoposide and melphalan]) showed the use of TBI was associated with a lower progression free survival [18].

BEAM +ATG and cyclophosphamide 200 mg/kg + ATG regimens were used from an early stage in MS treatment. Their acceptable safety profile has led to their continued use in recent clinical trials involving patients with highly active RRMS. These regimens are both recommended in the current guidelines of the EBMT Autoimmune Diseases Working Party (ADWP) guidelines [19]. A recent study has shown that using a conditioning regimen of busulfan, cyclophosphamide, and rabbit ATG (BuCy) with CD34+ cell selection caused complete suppression of disease with no relapses for up to 5 years post-transplant in all patients [20]. However, there was additional toxicity with this regimen, especially hepatic veno-occlusive disease, a serious complication associated with busulfan treatment, which was associated with one treatment related mortality out of the 24 patients studied. Retrospective registry data suggest that purging the graft off CD34+ cells has no added benefit to the transplant process, and is associated with a higher treatment related mortality [16].

Conditioning regimens still vary between treatment centres with no standardised regimen adopted as yet. As the intensity of a regimen increases so does the risk of side effects and potential treatment related mortality (TRM) [20]. The counter argument to lower intensity regimens is that they are less effective in suppressing disease activity resulting in increased rates of relapse and disease progression [21].

The most appropriate conditioning regimen to use in AHCT remains an unanswered question, with a number of other related questions including; the importance of central nervous system penetrance of the conditioning regimen chemotherapeutic agents and the level of chemotherapeutic drug concentration within the brain that can lead to the clearance of

pathological immune cells. These questions need to be addressed with an appropriate randomised study to identify the regimen with the best risk: benefit ratio.

Text box 1 highlights the different stages of an AHCT.

2.2 Mechanism of action

The exact mechanism by which AHCT stops disease activity in MS is yet to be fully established. By using a high dose of chemotherapy, a large proportion of the white cells, including pro-inflammatory cells, are destroyed in both blood and bone marrow, which may explain the early improvement in patients' condition.

Evidence for resetting of the immune system through T-cell receptor diversification, elimination of memory cells and thymic dependent generation of naïve and T-regulatory cells may explain the longer term effects of the AHCT on disease suppression [9]. AHCT does lead to the suppression of production of certain types of T-cell [22;23] but the balance between regulatory and pro-inflammatory lymphocytes is re-set in favour of regulatory cells [24].

Following AHCT patients have a greater diversity of naïve T-cells with reduction in memory cells [25] which may contribute to the development of immune tolerance [26]. These new T-cells are generated in the thymus, which goes through a period of increased activity after the AHCT [25]. This increased thymic activity contrasts with the reduced activity noted in untreated MS patients, and it is assumed that AHCT corrects this deficiency [27]. When patients fail to develop a diverse repertoire of naïve T-cells post-transplant, their response to treatment is likely to be less successful [28]. Figure 2 summaries the possible mechanisms underlying AHCT in MS.

2.3 Comparing AHCT to alternative disease modifying treatments (DMTs)

Only a handful of trials have directly compared the use of AHCT in MS with specific disease modifying therapies. The bulk of data are provided by observational cohort studies in which patients who fail to respond to standard disease modifying therapies are treated with AHCT. The observational nature of these studies has to be taken into account when interpreting the results. Tables 2 and 3 summarise relapse free survival and NEDA in different AHCT and DMT trials respectively. NEDA figures were not collected in the original DMT clinical trial studies, but subsequently calculated mainly by Sormani et al [29].

An international randomised controlled trial is being conducted to compare AHCT with other FDA approved DMT's (MIST Study [ClinicalTrials.gov Identifier: NCT00273364]) and is anticipated to provide further evidence on the efficacy of ACHT in MS

2.3.1 Interferon Beta and Glatiramer acetate

Interferon beta has multiple methods of action, including inhibiting leukocytes trisecting into the brain, modulating cytokine production and potentially inhibiting antigen presentation which results in its therapeutic effect in MS [30]. When compared with placebo, interferon beta has been shown to increase the time between relapses by between 3-5 months and decreases the risk of further relapse by 27-33% [31].

Glatiramer acetate, a modulator of T-cell differentiation [32] has a similar effect on relapse rate, but does not control MRI gadolinium enhancement in the early stages of treatment as well as interferon beta [33].

Although no study has looked specifically at how there two agents compare to AHCT, a grouped analysis from the EBMT showed that in patients who developed relapses whilst on a DMT (the vast majority of which were either on interferon or glatiramer acetate) disease

improvement or stabilisation could be achieved in 63% of patients at a median of 41.7 months post-transplant [16].

2.3.2 Natalizumab

Natalizumab is a humanised monoclonal antibody that targets the α4-subunit of α4β1-integrin, an adhesion molecule found on all leukocytes except neutrophils [34]. It works by preventing the migration of lymphocytes across the blood brain barrier. The two main randomised control trials for natalizumab (AFFIRM and SENTINEL) showed that it is very effective in reducing annualised relapse rate (0.81 to 0.26 in AFFIRM and 0.75 to 0.34 in SENTINEL). [34;35].

Initial trial data have been corroborated with follow up studies showing that natalizumab has sustained effects on reduction of relapse rate and progression of disability as measured by the EDSS for at least 2 years [36]. Over time, patients continue to experience progression of disability, albeit at a slower rate than prior to treatment.

The use of natalizumab has been associated with the JC-virus induced progressive multifocal leukoencephalopathy (PML). A recent report suggested that the prevalence of PML in patients treated with natalizumab is 2.1/1000 patients [37]. The risk factors for developing PML include the use of prior immunosuppressive drugs, the use of natalizumab for greater that 2 years and being JC-virus positive [37]. High levels of JC Antibody Index (1.5) are associated with the risk of PML as high as 1 in 263 patients [38].

No study as yet has compared AHCT directly with natalizumab. One study has looked at the efficacy of AHCT in patients with RRMS who have continued to have relapses whilst treated with disease modifying therapies, including natalizumab [23]. This study showed that at 3 years, the event free survival in patients treated with AHCT was 78.4% which is higher than

that reported in the AFFIRM study for natalizumab. A large North American cohort study of 145 patients (123 RRMS and 28 SPMS), who failed standard disease modifying therapies including natalizumab, found the 4-year relapse free survival rate with AHCT to be 80% and NEDA rate to be 68% [39]. A Swedish study of 48 patients (34 RRMS) who had aggressive disease and had failed conventional treatment, including natalizumab, found the relapse free survival rate to be 87% and a NEDA rate of 68% also [40]. The high NEDA rates seen in patients treated with AHCT is even more impressive when we consider that such patients generally have more active disease than those patients treated in trials for the other types of DMTs [41].

PML and JC virus infection are unlikely to be a long-term problem in AHCT treatment, as after the initial reconstitution of the immune system in AHCT, patients are not immunosuppressed unlike when they are treated with natalizumab. PML secondary to JC-Virus infection could theoretically be a problem in AHCT if the patient undergoing the treatment is a carrier of the JC-virus prior to the transplant. No study has reported infection with JC-Virus after AHCT currently.

2.3.3 Alemtuzumab

Alemtuzumab is a humanised anti-CD52 monoclonal antibody that depletes both B and T-lymphocytes changing a person adaptive immunity. Most studies assessing the efficacy of this drug compare the drug to interferon beta. In the CARE-MS-I trial, alemtuzumab was compared to interferon beta in patients with RRMS who had not previously had any disease modifying therapy for their MS [42]. At 2, years 78% of patients where relapse-free (interferon group 59%). NEDA rate were 39%. In the CARE-MS-II study patients were deemed suitable for trial entry when they had a relapse on interferon-beta [43]. At 2 years, 66% of patients were relapse free when compared to patients who had remained on

interferon-beta. NEDA rates in this study were 32%. This is significantly less than the relapse free rate of patients who have been treated with AHCT as highlighted above.

The main concern of using alemtuzumab is the development of autoimmune complications. One follow up study reported that 33% of patients developed autoimmune thyroid problems, 2.8% of patients developed immune thrombocytopenia and 0.46% developed anti-GBM antibodies after five years of follow up [44]. The development of anti-GBM antibodies is of particular concern as the vasculitis caused by these antibodies (Goodpasture's Syndrome) can lead to death in a significant number of cases. The main risk of developing a thyroid problem is within the first 3 years of drug initiation, the risk reducing after that.

Alemtuzumab has been incorporated as the T-cell depleting serotherapy in the conditioning regimen in some studies of AHCT in MS [13], but this was associated with an apparent increased risk of secondary autoimmune diseases compared with the use of rabbit anti-thymocyte globulin (rATG) in this context. Caution and further studies are warranted to fully assess the utility of alemtuzumab in the conditioning regimen but for the present time rATG continues to be the preferred serotherapy for the AHCT procedure.

2.3.4 Mitoxantrone

Mitoxantrone is a cytotoxic agent which works by stopping DNA repair through inhibiting topoisomerase activity. The drug has been shown to be useful in treating both RRMS and SPMS [45]. It is now very rarely used in MS therapy though due to concerns over its toxic side effects.

An early trial on AHCT compared Mitoxantrone to AHCT in patients with both RRMS and SPMS [46] had to be terminated due to poor recruitment. Although not powered to look for a difference in relapse rates in patients with RRMS or disease progression, it did show that the

number of gadolinium enhanced lesions in the brain of people with both SPMS and RRMS reduced significantly when comparing AHCT with Mitoxantrone.

2.3.5 Other Disease modifying agents

Limited specific data exist on how other disease modifying agents such as fingolimod and dimethyl fumarate compare to AHCT. Patients on these therapies have been treated with AHCT and included in some of the trials mentioned above. The control arm in the on-going MIST trial allows for patients to be treated with fingolimod or dimethyl fumarate.

2.3.6 Alternative Cell therapies

Other cell therapies similar to AHCT are also currently being developed to treat MS and other autoimmune diseases. One such therapy is mesenchymal stem (or stromal) cell (MSC) transplantation. This particular type of transplantation uses non-hematopoietic precursor cells, which can differentiate into mesodermal cell derivatives, but, perhaps more significantly, have immunomodulatory properties. Both autologous and allogeneic (third party donor, cord blood and placental) derived MSC have been studied as immunomodulatory treatments, although the place of MSC in autoimmune diseases, including MS remains to be clarified [47].

Allogeneic hematopoietic cell transplantation has also been used in MS patients, mainly those with another diagnosis which formed the main indication for the transplant [48]. Given that allogeneic transplantation results in replacement of an aberrant immune system, it appears to be effective in halting disease activity and potentially progression of autoimmune diseases. However, the substantial additional risks, including graft- versus-host disease and a substantial TRM risk, could rarely, if ever, be justified in MS.

2.4 Which MS patients should be offered AHCT

A review of a cohort of 151 patients showed that the use of AHCT was associated with an improvement of the EDSS scored in patients with RRMS who had the disease for 10 years or less compared to those with SPMS and a longer disease duration [39]. A small cohort study in the Czech Republic (n=26) found that AHCT has a more favourable outcome in patients who are not older than 35 years and have had the disease for less than 5 years [49]. Although the follow up period in this study was long (median 7 years), only a small number of patients where under the age of 35 (n=6).

Evidence of gadolinium enhancement on MRI prior to transplant is associated with a more favourable outcome [15;40]. Although AHCT is not normally offered to patients with significant long term fixed disabilities, EDSS score prior to AHCT treatment was reported not to be a good predictor of outcome [49]. This is thought to be the case for the number of DMTs used before AHCT [39].

It is known that MS has variable prevalence rates in different ethnic groups [50] although cohort studies from China have shown that AHCT has a similar effect on the disease when compared with studies done on North American and European populations [51].

Currently, HSCT is thought to be most effective in patients with RRMS who are 46 years or younger, have had the illness for less than 10 years and who have active disease clinically with evidence of enhancement on their MRI (See Table 4).

Various selection biases are inherent in published AHCT studies as a treatment for MS. Historically, the use of AHCT was reserved for younger patients with aggressive and potentially end stage disease where other treatments had failed. However with increasing experience, AHCT has been used earlier in the course of MS. Published studies are likely to

be biased towards younger age groups owing to the fact that such patients have the high level of general fitness needed for AHCT, and because relapsing remitting MS is very unlikely to present in older cohorts of patients. Further studies, including randomised controlled trials, are warranted to overcome such bias and inform decision making for patients at all ages and stages of MS. Reduced intensity conditioning regimens may be more appropriate for older and less fit patients.

2.5 Early and late complications of AHCT for MS

AHCT has intrinsic risks related to the toxicity of the high-dose conditioning treatment regimens and the temporary but profound cytopenia lasting for 1-2 weeks. Although some series have reported no treatment related mortality, retrospective multi-centre EBMT studies have been associated with a 100-day mortality of 1.3% [52] and high-intensity BuCy regimen used by Canadian investigators was associated with higher levels of toxicity [20]. Therefore, AHCT should be reserved for patients who have very active disease which has failed to respond to standard DMTs. With the exception of urinary tract infections, patients with MS seem to have similar complication rates during the acute treatment phase compared to patients with other hematopoietic and autoimmune diseases treated with AHCT [10;53].

Fever associated with ATG and post-transplant infection can exacerbate patients neurological symptoms during the early stages post-transplant [53;54]. This is thought to be secondary to conduction block in demyelinated neurones caused by the increased temperature. Non-infective pyrexia (temperature greater than $38.5^{o}C$) has also been shown to be associated with less favourable neurological outcomes post-AHCT. For this reason, steroids and paracetamol may be used after transplant to prevent or treat pyrexia, along with appropriate assessment and treatment of potential infections. Limiting fever during the per-transplant phase may help

prevent or resolve this Uthoff-like phenomenon, in the short term and there may be longer term benefits, which need to be confirmed [39].

Following AHCT some patients develop autoimmune hyper and hypothyroidism and thrombocytopenic purpura [13;39]. The rate of such autoimmune complications were higher when alemtuzumab (22.7%) rather than ATG (6.9%) was used in the conditioning regimen.

Secondary malignancy post-transplant has been reported following AHCT. In a cohort study of 151 patients underwent AHCT, one patient developed breast cancer and another developed lymphoma [39]. However, secondary malignancy appears to be rare following AHCT and MS patients who are managed with DMTs have an excess of malignancy. For example, two cases of papillary thyroid cancers were reported in the CARE-MS-1 study, giving a rate of 1% [42]. In the CARE-MS-II study 5 (1.3%) people developed malignancy in the alemtuzumab group compared to 2 (1%) in the interferon group [43].

Vigilance should be maintained post AHCT. A case of Epstein-Barr Virus related post-transplant lymphoproliferative disorder (EBV-PTLD) has been reported as the cause of death in one patient who received rATG in their conditioning regimen [10].

Herpes zoster is probably the commonest late infection post- AHCT in MS [40] and patients are often advised to stay on prophylactic acyclovir for at least a year post-transplant.

Gonadal failure and infertility need to be considered when counselling patients for AHCT. Patients should be offered cryopreservation of their ova/sperm prior to the procedure. Limited data about fertility post-AHCT are available. A cohort study of 48 patients (26 females) with MS reported a total of 8 pregnancies after treatment [40]. A total of 5 healthy infants were born whereas 2 pregnancies ended in miscarriage and one was ectopic. Of the patients who

had their ova/sperm cryopreserved both a male (n=1) and female (n=1) were able to produce a child.

Limited data are available on other long-term outcomes of AHCT in MS. The use of AHCT in other diseases is associated with cardiovascular, endocrine and musculoskeletal complications [55]. The risk of such complication in MS needs to be viewed in the light of the fact that in some of the rapidly progressive forms of MS, in which AHCT appears particularly effective, life expectancy can be in the order of weeks to months and associated with marked disability [56].

It is important that the transplant and neurology community continue to report the long-term outcomes of these patients so the late effects of AHCT can be fully evaluated in the MS population. The EBMT data registry and similar organisation provide a means of long term follow-up of both efficacy and late complications. Table 5 highlights some common complications reported in AHCT.

2.6 Future of AHCT in MS

As AHCT becoming a more mainstream therapy in the treatment of MS, certain questions remain unanswered. Compared with other DMTs, the risks of early mortality and morbidity from AHCT is relatively high, although this appears to have improved significantly over the last ten years, due to the use of safer conditioning regimens, better patient selection and increasing experience [39;40]

Although AHCT as a one-off treatment is likely to be more cost-effective than modern DMTs used, this will be need to be addressed prospectively in future studies [57].

Whether AHCT can cure MS remains to be seen. This treatment appears to be able to completely prevent recurrence of clinical relapses and MRI disease activity [20], halt disease

progression and improve disability scores in a significant number of patients [39]. Improvement in NEDA rates seen with the use of AHCT when compared to other disease modifying therapies is striking (see table 2 and 3). Long term follow up will be necessary to assess whether AHCT can cure in some patients.

3.0 Conclusions

AHCT has been used for the treatment of MS for over two decades. Cohort and small randomised studies showed that patients with RRMS form of MS have a better response and increasing experience has enabled safer delivery of this approach. Further long term follow up is needed before the benefits and safety of AHCT can be fully assessed. The use of AHCT in MS is not without risk and patients must be carefully selected. AHCT needs to be further refined and compared with the current standard of care for patients with RRMS in large randomised trials.

4.0 Expert Opinion

Although Autologous Hematopoietic Cell Transplantation (AHCT) has been used to treat MS since 1995, recent evidence from published case series and phase II clinical trials supports AHCT as an effective treatment for patients with highly active RRMS resistant to Disease Modifying Therapies. AHCT reduces clinical relapse rates, MRI disease activity and the progression of disability. In some patients, AHCT even reverses the disability caused by this illness. The best results are observed in young patients with short disease duration who have very active disease clinically and radiologically. AHCT has limited or no effect in patients in patients with progressive forms of MS.

AHCT is an intensive procedure involving high-dose chemotherapy and serotherapy with their inherent toxicities and should only be delivered in accredited centres where there is

close working between transplant haematologists and MS specialist neurologists. In experienced transplant centres the treatment-related risks have been minimised and are now considered justified in well-selected and motivated patients with highly active, treatment resistant RRMS, who would otherwise have a poor prognosis.

 Centres should follow international guidelines, such as those from the European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP), which provide recommendations for patient selection and regimens for stem cell mobilisation, transplantation and supportive care. Data reporting to the EBMT or other transplant registries is a mandatory requirement.

 Further data are needed to assess the long-term safety and efficacy of AHCT. The future place of AHCT in the MS treatment algorithm will need to be evaluated in the light of the outcome of the ongoing phase III MIST trial but it is likely to be an attractive and cost-effective second line therapeutic option for patients who have active RRMS who have failed a first line DMT. Even after MIST, further trials will be necessary to optimise the transplant regimen and compare AHCT against new DMTs.

 Destroying and rebuilding the abnormal immune system with AHCT will help improve our understanding of the role of the innate and adoptive immune systems in the pathogenesis of MS and has the potential to radically change the way in which treatment for MS is provided. The evolving translational approach to research in this field, combined with further therapeutic developments in the delivery of AHCT, have the potential to turn MS into a curable disease which no longer comes with a sentence of long term disability.

References

1. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990–2010: a descriptive study in the General Practice Research Database. Journal of Neurology, Neurosurgery, and Psychiatry. 2014;85(1):76-84.

2. Leary S, Giovannoni G, Howard R, Miller D. Multiple Sclerosis and Demyelinating Diseases. Neurology a Queen Square Textbook. Pp411-449.Blackwell Publishing. 2009.

3. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology. 2014;83(3):278-86.

4. Kurtzke, J. F. "Rating Neurologic Impairment in Multiple Sclerosis: An Expanded Disability Status Scale (Edss)." Neurology 33, no. 11 (1983): 1444-52.

5. Snowden JA, Patton WN, O'Donnell JL, Hannah EE, Hart DN. Prolonged remission of longstanding systemic lupus erythematosus after autologous bone marrow transplant for non-Hodgkin's lymphoma. Bone marrow transplantation. 1997;19(12):1247-50.

6. McAllister LD, Beatty PG, Rose J. Allogeneic bone marrow transplant for chronic myelogenous leukemia in a patient with multiple sclerosis. Bone marrow transplantation. 1997;19(4):395-7.

7. van Gelder, M. and D. W. van Bekkum. "Treatment of Relapsing Experimental Autoimmune Encephalomyelitis in Rats with Allogeneic Bone Marrow Transplantation from a Resistant Strain." Bone Marrow Transplant 16, no. 3 (1995): 343-51.

8. Fassas, A., A. Anagnostopoulos, A. Kazis, K. Kapinas, I. Sakellari, V. Kimiskidis and A. Tsompanakou. "Peripheral Blood Stem Cell Transplantation in the Treatment of Progressive Multiple Sclerosis: First Results of a Pilot Study." Bone Marrow Transplant 20, no. 8 (1997): 631-8.

9. Snowden JA. Rebooting autoimmunity with autologous HSCT. Blood. 2016;127(1):8-10.

10. Nash, R. A., J. D. Bowen, P. A. McSweeney, S. Z. Pavletic, K. R. Maravilla, M. S. Park, J. Storek, K. M. Sullivan, J. Al-Omaishi, J. R. Corboy, J. DiPersio, G. E. Georges, T. A. Gooley, L. A. Holmberg, C. F. LeMaistre, K. Ryan, H. Openshaw, J. Sunderhaus, R. Storb, J. Zunt and G. H. Kraft. "High-Dose Immunosuppressive Therapy and Autologous Peripheral Blood Stem Cell Transplantation for Severe Multiple Sclerosis." Blood 102, no. 7 (2003): 2364-72.

11. *Fassas A, Passweg JR, Anagnostopoulos A, Kazis A, Kozak T, Havrdova E, et al. Hematopoietic stem cell transplantation for multiple sclerosis. A retrospective multicenter study. Journal of neurology. 2002;249(8):1088-97. (First paper to show the used of AHCT in MS patients).

12. Samijn JPA, te Boekhorst PAW, Mondria T, van Doorn PA, Flach HZ, van der Meché FGA, et al. Intense T cell depletion followed by autologous bone marrow transplantation for severe multiple sclerosis. Journal of neurology, neurosurgery, and psychiatry. 2006;77(1):46-50.

13. Burt RK, Loh Y, Cohen B, Stefoski D, Balabanov R, Katsamakis G, et al. Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study. The Lancet Neurology. 2009;8(3):244-53.

14. Openshaw H, Lund BT, Kashyap A, Atkinson R, Sniecinski I, Weiner LP, et al. Peripheral blood stem cell transplantation in multiple sclerosis with busulfan and

cyclophosphamide conditioning: report of toxicity and immunological monitoring. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2000;6(5a):563-75.

15. Burt RK, Traynor AE, Pope R, Schroeder J, Cohen B, Karlin KH, et al. Treatment of autoimmune disease by intense immunosuppressive conditioning and autologous hematopoietic stem cell transplantation. Blood. 1998;92(10):3505-14.

16. Saccardi R, Kozak T, Bocelli-Tyndall C, Fassas A, Kazis A, Havrdova E, et al. Autologous stem cell transplantation for progressive multiple sclerosis: update of the European Group for Blood and Marrow Transplantation autoimmune diseases working party database. Multiple sclerosis (Houndmills, Basingstoke, England). 2006;12(6):814-23.

17. Burt RK, Cohen BA, Russell E, Spero K, Joshi A, Oyama Y, et al. Hematopoietic stem cell transplantation for progressive multiple sclerosis: failure of a total body irradiation-based conditioning regimen to prevent disease progression in patients with high disability scores. Blood. 2003;102(7):2373-8.

18. Reston JT, Uhl S, Treadwell JR, Nash RA, Schoelles K. Autologous hematopoietic cell transplantation for multiple sclerosis: a systematic review. Multiple sclerosis (Houndmills, Basingstoke, England). 2011;17(2):204-13.

19. Snowden JA, Saccardi R, Allez M, et al. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplantation. 2012;47(6):770-790. doi:10.1038/bmt.2011.185.

20. Curro D, Vuolo L, Gualandi F, Bacigalupo A, Roccatagliata L, Capello E, et al. Low intensity lympho-ablative regimen followed by autologous hematopoietic stem cell

transplantation in severe forms of multiple sclerosis: A MRI-based clinical study. Multiple sclerosis (Houndmills, Basingstoke, England). 2015;21(11):1423-30.

21. **Atkins HL, Bowman M, Allan D, Anstee G, Arnold DL, Bar-Or A, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. The Lancet. Published Online June 9, 2016 DOI: http://dx.doi.org/10.1016/S0140-6736(16)30169-6. (This is the first paper to show complete suppression of the immune response in MS after treatment with AHCT).

22. Darlington PJ, Touil T, Doucet JS, Gaucher D, Zeidan J, Gauchat D, et al. Diminished Th17 (not Th1) responses underlie multiple sclerosis disease abrogation after hematopoietic stem cell transplantation. Annals of neurology. 2013;73(3):341-54.

23. **Nash RA, Hutton GJ, Racke MK, Popat U, Devine SM, Griffith LM, et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for relapsing-remitting multiple sclerosis (HALT-MS): a 3-year interim report. JAMA neurology. 2015;72(2):159-69. (First randomised control trial for use of AHCT in RRMS)

24. Abrahamsson SV, Angelini DF, Dubinsky AN, Morel E, Oh U, Jones JL, et al. Non-myeloablative autologous haematopoietic stem cell transplantation expands regulatory cells and depletes IL-17 producing mucosal-associated invariant T cells in multiple sclerosis. Brain : a journal of neurology. 2013;136(Pt 9):2888-903.

25. Muraro PA, Douek DC, Packer A, Chung K, Guenaga FJ, Cassiani-Ingoni R, et al. Thymic output generates a new and diverse TCR repertoire after autologous stem cell transplantation in multiple sclerosis patients. The Journal of Experimental Medicine. 2005;201(5):805-16.

26. Berzins SP, Uldrich AP, Sutherland JS, Gill J, Miller JF, Godfrey DI, et al. Thymic regeneration: teaching an old immune system new tricks. Trends in molecular medicine. 2002;8(10):469-76.

27. Hug A, Korporal M, Schroder I, Haas J, Glatz K, Storch-Hagenlocher B, et al. Thymic export function and T cell homeostasis in patients with relapsing remitting multiple sclerosis. Journal of immunology (Baltimore, Md : 1950). 2003;171(1):432-7.

28. *Muraro PA, Robins H, Malhotra S, Howell M, Phippard D, Desmarais C, et al. T cell repertoire following autologous stem cell transplantation for multiple sclerosis. The Journal of clinical investigation. 2014;124(3):1168-72. (Study showing potential mechanism by which AHCT works in MS)

29. Sormani MP, Muraro PA, Saccardi R, Mancardi G. NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. Multiple sclerosis (Houndmills, Basingstoke, England). 2016.

30. Yong, V. W., S. Chabot, O. Stuve and G. Williams. "Interferon Beta in the Treatment of Multiple Sclerosis: Mechanisms of Action." Neurology 51, no. 3 (1998): 682-9.

31. Ebers et al "Randomised Double-Blind Placebo-Controlled Study of Interferon Beta-1a in Relapsing/Remitting Multiple Sclerosis. Prisms (Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis) Study Group." Lancet 352, no. 9139 (1998): 1498-504.

32. Weber MS, Hohlfeld R, Zamvil SS. Mechanism of action of glatiramer acetate in treatment of multiple sclerosis. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics. 2007;4(4):647-53.

33. La Mantia, L., C. Di Pietrantonj, M. Rovaris, G. Rigon, S. Frau, F. Berardo, A. Gandini, A. Longobardi, B. Weinstock-Guttman and A. Vaona. "Interferons-Beta

Versus Glatiramer Acetate for Relapsing-Remitting Multiple Sclerosis." Cochrane Database Syst Rev 7, (2014): CD009333.

34. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. The New England journal of medicine. 2006;354(9):911-23.

35. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. The New England journal of medicine. 2006;354(9):899-910.

36. Butzkueven H, Kappos L, Pellegrini F, Trojano M, Wiendl H, Patel RN, et al. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results. Journal of neurology, neurosurgery, and psychiatry. 2014;85(11):1190-7.

37. Planas R, Martin R, Sospedra M. Long-term safety and efficacy of natalizumab in relapsing-remitting multiple sclerosis: impact on quality of life. Patient related outcome measures. 2014;5:25-33.

38. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. The New England journal of medicine. 2012;366(20):1870-80.

39. **Burt RK, Balabanov R, Han X, Sharrack B, Morgan A, Quigley K, et al. Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis. JAMA. 2015;313(3):275-84. (Largest case series published to date of patients with RRMS who have been treated with AHCT).

40. **Burman J, Iacobaeus E, Svenningsson A, Lycke J, Gunnarsson M, Nilsson P, et al. Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis:

the Swedish experience. Journal of neurology, neurosurgery, and psychiatry. 2014;85(10):1116-21. (One of the largest studies showing the benefit of AHCT use in RRMS).

41. Sormani MP, Muraro PA, Saccardi R, Mancardi G. NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. Multiple sclerosis (Houndmills, Basingstoke, England). 2016.

42. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet (London, England). 2012;380(9856):1819-28.

43. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet (London, England). 2012;380(9856):1829-39.

44. Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, et al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 clinical trial. Neurology. 2012;78(14):1069-78.

45. Martinelli Boneschi F, Rovaris M, Capra R, Comi G. Mitoxantrone for multiple sclerosis. The Cochrane database of systematic reviews. 2005(4):Cd002127.

46. Mancardi GL, Sormani MP, Gualandi F, Saiz A, Carreras E, Merelli E, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial. Neurology. 2015;84(10):981-8.

47. Cohen JA. Mesenchymal stem cell transplantation in multiple sclerosis. Journal of the neurological sciences. 2013;333(1-2):43-9.

48. Hinterberger W, Hinterberger-Fischer M, Marmont A. Clinically demonstrable anti-autoimmunity mediated by allogeneic immune cells favorably affects outcome after stem cell transplantation in human autoimmune diseases. Bone marrow transplantation. 2002;30(11):753-9.

49. Krasulova, E., M. Trneny, T. Kozak, B. Vackova, D. Pohlreich, D. Kemlink, P. Kobylka, I. Kovarova, P. Lhotakova and E. Havrdova. "High-Dose Immunoablation with Autologous Haematopoietic Stem Cell Transplantation in Aggressive Multiple Sclerosis: A Single Centre 10-Year Experience." Mult Scler 16, no. 6 (2010): 685-93.

50. Langer-Gould A, Brara SM, Beaber BE, Zhang JL. Incidence of multiple sclerosis in multiple racial and ethnic groups. Neurology. 2013;80(19):1734-9.

51. Ni XS, Ouyang J, Zhu WH, Wang C, Chen B. Autologous hematopoietic stem cell transplantation for progressive multiple sclerosis: report of efficacy and safety at three yr of follow up in 21 patients. Clinical transplantation. 2006;20(4):485-9.

52. Mancardi G, Saccardi R. Autologous haematopoietic stem-cell transplantation in multiple sclerosis. The Lancet Neurology. 2008;7(7):626-36.

53. Atkins, Harold L., and Mark S. Freedman. "Hematopoietic Stem Cell Therapy for Multiple Sclerosis: Top 10 Lessons Learned." Neurotherapeutics 10.1 (2013): 68–76.

54. Morris ES, Sharrack B, Dalley CD, Snowden JA. The Uhthoff phenomenon: a potential post transplant complication in advanced progressive multiple sclerosis. Bone marrow transplantation. 2007;40(10):1003-4.

55. Bhatia S. Long-term health impacts of hematopoietic stem cell transplantation inform recommendations for follow-up. Expert review of hematology. 2011;4(4):437-54.

56. Johnson MD, Lavin P, Whetsell WO, Jr. Fulminant monophasic multiple sclerosis, Marburg's type. Journal of neurology, neurosurgery, and psychiatry. 1990;53(10):918-21.

57. Tappenden P, Saccardi R, Confavreux C, Sharrack B, Muraro PA, Mancardi GL, et al. Autologous haematopoietic stem cell transplantation for secondary progressive multiple sclerosis: an exploratory cost-effectiveness analysis. Bone marrow transplantation. 2010;45(6):1014-21.

EDSS Score	
0.0	Normal neurological exam
1.0	No disability, minimal signs in more than one FS

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SMB, BS and JS have nothing to disclose

Figure Legends

Figure 1: This figure highlights the new classification structure for MS used in clinical trials as suggested by Lublin et al 2014 [3]. * Active disease refers to the presence of a relapse or measureable active disease on MRI imaging. ** Progression refers to a sustained change in the patients EDSS over a set time period, often longer than 6 months.

Figure 2: This figure highlights the possible biochemical changes to the immune system that may explain why AHCT halts MS.

1.5	Minimal disability in one FS
2.0	Minimal disability in two FS
2.5	Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
3.0	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions);
5.5	Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting;
7.0	Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day.
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms.
8.5	Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions
9.0	Helpless bed patient; can communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

Table 1: The Kurtzke Expanded Disability Status Scale (EDSS) this scale is often used in MS research to monitor progression of the disease. **FS** stands for functional status. The overall EDSS score is calculated from different parts or the neurological exam. Each of these give a FS which is then used to calculate the EDSS.

BOX 1: PHASES OF THE AHSCT PROCEDURE

1. **Mobilisation and harvest**. In the first stage the patient is given a short course of granulocyte-colony stimulating factor (G-CSF) which releases hematopoietic stem cells into the peripheral circulation. Most centres performing this step will supplement the G-CSF infusion with chemotherapy, often cyclophosphamide 2-4g/m2, which not only mobilises the stem cells for harvest by apheresis but also provides some interim suppression of disease activity.

2. **Conditioning and stem cell re-infusion**. In this stage the patient is given a high dose of cytotoxic therapy (i.e. chemotherapy, radiotherapy and/or serotherapy, such as ATG or monoclonal antibodies such as alemtuzumab) to eliminate the majority, if not all, of their bone marrow and immune system. Conditioning regimens can be of differing intensities, as described above.

3. **Following conditioning**, the stem cells collected in the mobilisation stage are re-infused into the patient. Engraftment is confirmed when the patient starts producing peripheral blood cells again.

Text Box 1

Table 2: Shows outcomes from various cohort studies and trials performed concerning MS patients who have undergone AHCT. **NCG** means No Comparator Group as this was a cohort study. ** In the Burman 2014 study 8 patients where included that did not have RRMS and instead had a diagnosis of SPMS. † Burt 2015 is a follow up study that uses the same patients that are in Burt 2009, but with increased recruitment.

Table 3: * indicates that the data was not displayed. † refers to patients taking 1.24mg of Fingolimod.

Study	Number of Patients	Relapse Free survival at one year	New Gad positive MRI Lesions at 1 year	EDSS change at one year median	NEDA (No evidence of disease activity)	Conditioning Regimen	Justification for AHCT	Notes
Burman 2014	48	87% at 5 years	8 new lesions in entire cohort during all follow up	-0.75 (All patients) -1.5 (Progressive patients excluded)	68% at 5 years	BEAM/ATG (n=41) Cyclophosphamide /ATG (n=7)	Patients treated as rescue therapy for severe RRMS**	Cohort study based on responses to a survey
HALT-MS Nash 2015	24	86.3% at 3 years	0 at 3 years 2 patients developed lesion thereafter	-0.5 at 3 years	78.4% at 3 years	BEAM/ATG	failure of DMT (2 or more clinical relapses during past 18 months associated with increased EDSS score.	Single arm phase 2 clinical trail (HALT-MS)
Burt 2009	21	62% at 3 years	5 patients by end of follow up (3 years)	-0.9 at 1 year and -1.7 at 4 years	62% at 3 years	Cyclophosphmide/Mesa/ Alemtuzumab/ Methylprednisolone	interferon beta treatment plus corticosteroid-treated relapses last 12 months, or 1 relapse and gadolinium-enhancing lesions seen on MRI.	Prospective Cohort Study
Burt 2015†	145	89% at 2 years and 80% at 4 years	*	-1.0 at 1 year and -1.5 at 5 years	68% at 4 years	Cyclophosphomide plus with Alemtuzumab or ATG.	interferon beta treatment plus corticosteroid-treated relapses last 12 months, or 1 relapse and	Observational Cohort Study

							gadolinium-enhancing lesions seen on MRI.	
Shechenko 2008	45	*	None in patients who did not have relapse	28 patients had a drop of EDSS of 0.5 at 6 months	*	BEAM/ATG	Confirmed diagnosis of MS with an EDSS between 1.5-8.0.	Prospective Cohort Study

Study	Number of Patients	Relapse Free survival at one year	New Gad positive MRI Lesions at 1 year	EDSS change at one year median	NEDA (No evidence of disease activity)	Notes
AFFIRM Polman 2006	627	68% reduction in relapse rate compared to placebo	245 patients had at least one new lesion	*	37% at 2 years	Randomised control trial
CARE-MS-1 Cohen 2012	386	77.6% at 2 years	176 patient had new of enlarging lesions at 2 years	-0.14 at 2 years	39% at 2 years	Randomised control trial
CARE-MS-II Coles 2012	436	65% at 2 years	186 patient had new lesions at 2 years	-0.17 at 2 years	32% at 2 years	Randomised control trial
FREEDOM Kappos 2010	854	60% in relapse rate compared to placebo†	35 patients had new lesions at 2 years†.	-0.03 at 2 years†	48% at 2 years	Randomised control trial

Favourable outcome for AHCT in MS is seen in
• **RRMS**
• **Young patients (<_45 years)**
• **Short disease duration (<_10 years)**
• **Active disease (two or more relapses in 12 months in the preceding 12 months)**
• **Evidence of Gadolinium enhancement on MRI scans**

Table 4: factors that are associated with a more favourable outcome after AHCT in MS.

Study	Number of Deaths secondary to AHCT	Infection Rate	Other complications	Mean Length of Follow up
Burman 2014	No Deaths	17 Neutropenic fever 8 Herpes Zoster Infections 3 Clostridium Difficile 1 Candida	4 Hypothyroid disease 1 Crohn's Disease 1 Alopecia areata 1 Incontractable Epilepsy 1 Deep Vein Thrombosis	47.4 months
HALT-MS Nash 2015	2 Deaths one secondary to asthma and one secondary to MS progression	16 Neutropenic fevers 1Clostridium Difficile	3 Deep Vein thrombosis 1 Pulmonary Embolism	46.5 Months (Median)
Burt 2009	No Deaths	5 neutropenic fevers 2 Zoster infections 1Clostridium Difficile	2 Immune thrombocytopenia	37 Months
Burt 2015†	No Deaths	4 Clostridium Difficile	7 Immune thrombocytopenia 7 Thyroid disease	30 Months
Shechenko 2008	1 death due to intracranial haemorrhage	*	*	19 Months

Table 5: This table shows the common side effects reported in each of the main AHCT studies post transplant. * indicates that this information was not in this particular study.

Article Highlights;

- Originally supported by animal models and serendipitous case reports, AHSCT has been used in multiple sclerosis since 1995. AHSCT is an intensive procedure involving high-dose chemotherapy and serotherapy with their intrinsic risks.

- Although it has a limited effect on progressive forms of multiple sclerosis, in relapsing remitting multiple sclerosis AHSCT appears to reduce clinical relapses and MRI disease activity and halt the progression of disability. NEDA rates after treatment with AHSCT appear to much higher than any other MS disease modifying therapy, although randomised controlled trial data is awaited.

- AHSCT appears to work through an immediate debulking of neuro-inflammation followed by longer-term modulation of the immune system, with re-diversification and renewal of T cell populations, including T-regulatory cells.

- Further work needs to focus around the long term effects of use of AHSCT in MS.