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REVIEW ARTICLE

Cell Therapy for Multiple Sclerosis

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Abstract Cell therapy is considered a promising potential treatment for multiple sclerosis, perhaps particularly for the progressive form of the disease for which there are currently no useful treatments. Over the past two decades or more, much progress has been made in understanding the biology of MS and in the experimental development of cell therapy for this disease. Three quite distinct forms of cell therapy are currently being pursued. The first seeks to use stem cells to replace damaged myelin-forming oligodendrocytes within the CNS; the second aims, in effect, to replace the individual's misfunctioning immune system, making use of haematopoietic stem cells; and the third seeks to utilise endogenous stem cell populations by mobilisation with or without in vitro expansion, exploiting their various reparative and neuroprotective properties. In this article we review progress in these three separate areas, summarising the experimental background and clinical progress thus far made.

Key Points

There are three current approaches to cell therapy in multiple sclerosis, each at different stages of development.

Oligodendrocyte replacement aims to use stem cells, usually autologous-induced pluripotent stem cells, to replenish damaged myelin-forming cells; this has not yet translated from laboratory studies to the clinic.

Autologous haematopoietic stem cell (HSC) transplantation involves near-ablation or major suppression of the patient's haematopoietic system followed by replacement using previously harvested HSCs aiming to reconstitute or 'reboot' the immune system; this is at the phase III stage of clinical trials.

The third approach aims to supplement endogenous repair (and neuroprotective mechanisms) by infusing autologous reparative stem cells, such as multipotent mesenchymal stem cells from the bone marrow, and/or related subpopulations; a number of phase II single- and multicentred trials are currently underway exploring this approach.

1 Introduction

Multiple sclerosis (MS) is an autoimmune, inflammatory demyelinating condition. T-helper (Th) cells and antigen-presenting cells ultimately coordinate the production of inflammatory cytokines and chemokines within the central nervous system (CNS) parenchyma, leading to recruitment

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of other proinflammatory mediators and, finally, destruction of the myelin sheath and axons [1]. Axonal loss presents a key pathophysiological mechanism of progressive disease, and progressive axonal damage is likely to be due to a combination of persistent myelin and oligodendrocyte loss (causing loss or trophic support and sustained demyelination-induced conduction block) and continued exposure to injurious agents [2].

MS affects some 2.5 million people worldwide. More than 80% of patients ultimately develop progressive disability, despite commencing with a relapsing-remitting course, with a median time to progression of 15 years [3]. Ten to 20% of patients have a primary progressive (PPMS) course [4]. The costs of MS increase dramatically with increasing disability and impairment [5]. In stark contrast to relapsing-remitting disease, for which there is a wide and still increasing choice of drugs, there are no conventional treatments that offer significant efficacy in preventing or reversing the accumulation of disability [6]. As with many other neurodegenerative conditions, the potential of cell therapies has been explored over the last few decades with efforts to translate in vitro and in vivo experimental studies to safety and feasibility trials. Nonetheless, the challenges facing the development of cell therapy for the treatment of MS remain daunting.

MS is generally accepted to be an autoimmune disease, with oligodendrocytes and the myelin sheaths they synthesise and support representing the primary target of this autoimmunity, although much remains poorly understood. Not least, we do not know what triggers the disease. We also do not know why inflammation occurs in patches in the CNS, rather than diffusely, nor why some areas of the brain and spinal cord are more susceptible than others. Perhaps least of all do we understand how this patchy inflammatory demyelination relates to the progressive neuronal and axon loss that underlies the progressive disability occurring in most patients with MS, a phase of the disease that has the pace and features far more suggestive of a degenerative than inflammatory condition. These areas of significant uncertainty clearly impede the development of rational therapies, cell-based and otherwise. A further challenge is the lack of clinically relevant experimental models of disease; experimental autoimmune encephalomyelitis (EAE) models are usually characterised by relapses with rapid recovery of inflammatory damage but no progressive neurodegenerative phase, and models of focal, chemically-induced demyelination demonstrate little or no inflammation. Additional major challenges are presented by the variability of disease features and course, and also the insensitivity of generic clinical outcome measures [7].

The complexity of the disease also helps to explain the complexity of current approaches to cell therapy in MS. There are three quite different types of cell therapy being actively explored, invariably aiming to exploit the therapeutic properties of different stem cells to achieve inhibition of the immune pathogenesis of disease, neuroprotection and to promote repair. This review will present an overview of the current position of cell therapy in MS.

2 Approaches to Cell Therapy in Multiple Sclerosis

2.1 Replacing Oligodendrocytes

In 1977, it was shown that exogenous myelinating cells injected into demyelinated lesions in the rodent CNS achieved successful remyelination [8]. Transplantation of myelin-forming cells, either directly into magnetic resonance imaging (MRI)-disclosed lesions or with the intention of their dissemination through the entire neuro-axis, has been a major aim ever since [9]. In a variety of experimental paradigms, many types of transplanted cell have successfully remyelinated acute focal demyelinated lesions in the adult CNS [10].

Until recently, embryonic stem cells were considered the best putative candidates for such an approach; however, it is now clear that human dermal fibroblasts and other somatic cells can be reprogrammed to pluripotency via retroviral transduction [induced pluripotent stem cells (iPSCs)]. More recently, the same has been achieved by chemical or pharmacological approaches. MS patient-derived iPSCs can differentiate into oligodendrocytes (as well as astrocytes and neurons) with normal karyotypes, and these can then achieve myelination in vivo in the *shiverer* mouse [11]. IPSCs are probably now the more favoured cell type for oligodendrocyte replacement, although the protocol for induction is inefficient, and concerns remain about genomic stability and the tumour risk associated with using these cells therapeutically [12].

In addition, however, there are conceptual difficulties with this approach. Both oligodendrocyte progenitors and neural precursors are in fact present in significant numbers in MS lesions, yet they are unable to regenerate myelin, perhaps as they are unable to differentiate, and show arrested development [3]. It is not clear that adding more cells would help under these circumstances. Additionally, while inflammatory demyelinating lesions cause relapse-related neurological dysfunction, their direct relationship to chronic progressive disability is unclear and uncertain; neither lesion load, lesion site, nor the number of relapses correlate well with chronic disability [3]. It has therefore become difficult to see how patients with secondary or primary progressive disease might benefit from directly

injecting oligodendrocyte progenitors into MRI-disclosed lesions [3], although a case might still occasionally be made in patients with very large lesions causing relapse-related symptoms who may develop disability as a direct effect of significantly incomplete spontaneous remyelination.

However, what is undeniable is that the intensive study of the molecular and cellular neurobiology of myelin repair stimulated by, and originally directed towards, oligodendrocyte replacement therapy has yielded invaluable new knowledge relating to remyelination, knowledge that has directly lead to molecular candidates for promoting myelin repair—either small molecules as conventional pharmacological agents or monoclonal antibodies, several of which are now undergoing early-phase clinical trials [13].

2.2 Autologous Haematopoietic Stem Cell Transplantation

Autologous haematopoietic stem cell transplantation (AHSCT) is a promising treatment for MS, perhaps particularly for those who have not responded to conventional immune therapies [14]. AHSCT is a well-established procedure for the treatment of poor prognosis haematological malignancies, and, in the last 20 years, it has been explored to treat patients with severe autoimmune diseases refractory to standard treatments [15]. The rationale for this approach is that ablation of the aberrant immune system followed by reconstitution of a 'new' immune system from haematopoietic stem cells (HSCs) should substantially alter the characteristics of T-cell responses and other immune reactivities, and therefore potentially improve the clinical course of autoimmunity, including aberrant immune responsivity in MS [16]. Following early reports such as that from Fassas et al. [17], MS has become one of the most common autoimmune diseases to be treated with AHSCT [18]. In 1997, the Autoimmune Diseases Working Directive (ADWP) of the European Group for Blood and Marrow Transplantation (EBMT) set guidelines for application of AHSCT to autoimmune disease and advised that all cases treated should be registered within the EBMT database [19]. Over 2000 patients with an autoimmune disorder have now been reported to the registry of the EBMT as having been so treated, more than 800 of whom had MS.

Commonly, the source of stem cells is bone marrow or peripheral blood. Peripheral blood as a source has the advantage of ease of collection (compared with bone marrow aspiration), but since the normal numbers of circulating stem cells are small, stem cells must first be mobilised from the bone marrow using cyclophosphamide or growth factors such as granulocyte colony-stimulating factor (G-CSF). The combination of cyclophosphamide and G-CSF is generally preferred as cyclophosphamide reduces the potential risk of MS exacerbation in response of G-CSF, while the inclusion of cyclophosphamide in the mobilisation regimen decreases the number of T cells in the apheresis collection [20].

Once harvested, HSCs can be manipulated by either CD34+ positive selection for lymphocyte depletion and/or directly purged with antilymphocyte antibodies (such as with CAMPATH 1H or cytotoxic agents) [21]. HSCs carry the CD34 and Thy-1 surface markers, which are usually used to isolate cells, including early progenitors [21].

Having collected and prepared HSCs for transfusion, the patient's own immune system must be ablated, or at least suppressed sufficiently to allow the infused HSCs to regenerate the immune system in preference to the 'original' immune system reasserting itself. This process is known as 'conditioning'; different conditioning regimens can be administered before the infusion of CD34+ autologous cells [22], and the patient is usually admitted for conditioning. Common regimens utilised vary in intensity. Examples include:

- High-intensity regimens include total body irradiation (TBI) or high-dose busulfan;
- Low-intensity conditioning regimens with cyclophosphamide alone, melphalan alone, or fludarabine-based regimens;
- Intermediate-intensity regimens include other combinations such as BEAM (see below), or antithymocyte globulin (ATG) and cyclophosphamide [23].

The combined carmustine (**Bi**CNU®), **E**toposide, cytarabine (**Ara**C) and **M**elphalan (BEAM) conditioning regimen is considered the most effective [16]. According to the EBMT, the risk of transplant-related mortality (TRM) in HSCT, defined as deaths occurring in the first 100 days [24], has decreased since the year 2001, likely due at least in part to the avoidance of aggressive conditioning regimens that resulted in toxicity, such as the use of busulfan [20].

Finally, following the conditioning stage, at least 2×10^6 CD34+ positive cells/kg of body weight is required for haematological reconstitution [21]. Haematological recovery requires a mean of 12 days to reach a neutrophil count >500/μl, and 10 days to reach a platelet count of $>20 \times 10^9$ [22].

HSCT has also been shown to normalise immunoregulatory gene expression, thereby improving the immunoregulatory network [25, 26]. AHSCT induces profound modifications in the immune regulatory compartment, such as a transient increase in regulatory FoxP3+T cells [22]. In MS, AHSCT renews the CD4+ repertoire, blunts the encephalitogenic effector response by reducing Tc17 and Th17 peripheral blood T cells, impairs

antigen presentation, and increases the numbers of immune regulatory cells [22].

Conversely, autopsy material from five MS patients who received AHSCT showed that there was ongoing evidence of active demyelination, while the inflammatory infiltrate within the lesions showed predominantly CD8+ cytotoxic T cells, with high numbers of acutely damaged axons. This implies that despite AHSCT (and the accompanying immunosuppression), there is ongoing disease activity, arguably also reflected in patients exhibiting continued disease progression and/or MRI activity in AHSCT trials [27]. AHSCT has also been associated with rapid brain volume loss in the months subsequent to treatment, the rate of which then declines after 2 years. The initial loss may be due to resolution of the oedema and inflammation associated with pretransplant disease activity, or relate to the intense immune ablative conditioning procedure [28].

Nonetheless, it seems clear that AHSCT can reduce clinical relapse activity dramatically, with a potency comparable with (or, it has been claimed, superior to) the current most powerful licensed therapies, alemtuzumab and natalizumab. However, its morbidity and mortality may be greater, therefore the place of AHSCT in the overall treatment paradigm of relapsing-remitting MS (RRMS) remains to be defined. Comparative studies are required.

2.3 Mesenchymal Stromal Cells (MSCs) and Related Cells

In addition to HSCs, bone marrow contains other cell types with stem cell-like properties, including mesenchymal stromal cells. Many stem cell researchers concentrate on these cells because of their ability to promote cell repair through multiple mechanisms, combined with immune-modulating and immune-suppressive actions. Mesenchymal stromal cells (MSCs) can stimulate local proliferation of endogenous neural precursors, secrete various trophic factors and protective antioxidants such as superoxide dismustase-3, reduce gliotic scar formation, and promote CNS neurite outgrowth and remodelling [3, 29, 30].

MSCs are a rare and heterogeneous population of cells that are relatively easy to extract and expand from a number of tissues in the body, including bone marrow. They were first described in the 1970s by Friedenstein [31]. No single marker, or even combinations of markers, specifically identify MSCs. Criteria for identification proposed by the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy include plastic adherence during in vitro expansion, absence of haematopoietic surface markers (such as CD45 and CD34), the presence of CD73, CD90 and CD105 surface markers, and the ability to undergo in vitro differentiation into adipocytes, chondroblasts and osteoblasts [32]. The normal local function of MSCs is to support HSCs within the bone marrow niche, but they also have a systemic role, following release into the circulation, in maintaining vascular and immunological homeostasis and facilitating tissue repair [33]. They have a selective ability to home to sites of tissue damage or inflammation, a process mediated by chemokine receptors and other adhesion molecules [1].

MSCs have a number of immunomodulatory properties, such as suppression of T cells leading to a concomitant increase in the Th2 cytokine IL4 [34]. Furthermore, MSCs can promote self-tolerance by inhibiting the ability of dendritic cells to become antigen-presenting cells [12].

MSCs also have a number of neuroprotective properties. They promote oligodendrogliogenesis, neural survival and neurite outgrowth, and protect neurons against oxidative stress, partly through the secretion of neurotrophins such as brain-derived neurotrophic factor and nerve growth factor [29, 35]. Rather remarkably, they can also protect tissue by directly transferring mitochondria to vulnerable cells through a process involving membrane fusion [36], and can also fuse with cells to promote target cell survival [37].

MSCs therefore offer potential therapeutic benefit in MS by restricting inflammation, protecting axons, neurons and glia, and promoting remyelination [38]. Systemic transplantation of autologous or allogeneic MSCs in relapsing-remitting or progressive models of EAE results in a decrease in T- and B-cell responses, accompanied by clinical and histological improvements, a reduced number of inflammatory lesions, and reduced axonal loss with preservation of myelin structure [39, 40]. Immunological analysis discloses an increase in the proportion of CD4+CD25+ regulatory T cells, a decrease in the proliferative responses of lymphocytes, and expression of CD40+, CD83+, CD86+ and human leukocyte antigen–antigen D related (HLA-DR) on myeloid dendritic cells 24 h after MSC transplantation [41].

There are a number of theoretic risks in the application of MSCs, including the possibility of pulmonary embolic phenomena. Close monitoring during infusion is necessary because of potential toxicity related to dimethyl sulfoxide (DMSO) in the freezing medium. The use of fetal bovine serum (FBS) during MSC preparation (in the cell culture medium) raises issues. For example, anti-FBS antibodies might react with FBS antigens adherent to MSCs, leading to rejection or infusion-related allergic reactions. FBS could also theoretically transmit infection, including zoonoses such as bovine spongiform encephalopathy [42, 43]. Therefore, the development of serum-free culture methods is a priority. Culture-expanded MSCs can trigger a so-named 'instant blood-mediated inflammatory reaction' (IBMIR), mediated by the innate immune system [33, 43, 44]. A further infection risk comes with ex vivo

expansion, and this also may enhance the possibility of ectopic tissue formation. When culture-expanded MSCs were administered intraventricularly, they migrated into the brain parenchyma and formed cellular masses with focal inflammation. Local tissue damage and collagen-fibronectin deposition were observed [45]. Cancer related to malignant transformation of culture-expanded MSCs or permissive effects of immunosuppression is also a theoretical concern [33]. In vivo, MSC transplantation could conceivably have pro- or anti-inflammatory effects in MS [46]; suppressing the 'wrong' component of the immune system, or precipitating (perhaps by some allergy-related mechanism) a general increase in immune activation, could conceivably exacerbate RRMS. One recent report described a patient with MS who developed acute disseminated encephalomyelitis-like illness 6 h after the third of three monthly intrathecal injections of autologous MSCs [47].

The optimal route and dose of MSC administration is still debated. If we assume that the cells are required to access the CNS to be clinically effective, a drawback of intravenous administration of MSCs is that cells will become trapped in the lungs or will home to lymph nodes and other tissues, reducing the number of cells available to migrate to the CNS [41]. An intrathecal approach for cell-based therapies in neurological disease such as MS, in which areas of tissue damage are widespread throughout the neuro-axis, may appear to increase the likelihood of migration of the injected cells to the closer proximity of areas of CNS damage. The injected cells may circulate with the flow of cerebrospinal fluid and therefore gain a better chance of reaching the affected areas [41]; however, intrathecal delivery of MSCs is complicated by a common meningeal reaction. Very little evidence is available on formal dosing of MSCs for transplantation; a commonly used dosage is 1–2 $\times$ 10^6 cells/kg [33].

The extent of engraftment and duration of survival of donor MSCs after transplantation in humans is largely unknown. Autopsies of 18 patients who received HLA-mismatched MSCs for complications of HSCT showed little evidence of MSC DNA in donor tissue [48]. Engraftment and magnitude of therapeutic response correlate poorly, and a paracrine effect with persistent therapeutic benefit that is not dependent on surviving implanted cells is postulated for some treatment effects—the so-called 'hit and run' mechanism of action. While sustained beyond the duration of cell 'residence', such effects are ultimately likely to subside, therefore repeated administration may be required. Harris et al. found that multiple administration of MSCs in a rodent inflammatory demyelination model was more likely to help arrest progression [49]; however, the risk of sensitisation would likely confine such an approach to autologous MSCs [33]—repeated administration of allogeneic MSCs does generate problematic immune reactivity [50]. The possibility that recurrent administration of autologous MSCs may be required raises further practical questions. Would these be achieved by repeated harvests, or perhaps through expansion with cryopreservation? Before culture-expanded MSCs can be seen as an 'off-the-shelf' product [33], comprehensive certification of the donor would be required to rule out infection and cancer. Regulatory hurdles would be more difficult.

We do not know whether autologous or allogenic MSCs might be more effective. There is a theoretical concern that autologous cells from a patient with an inflammatory and degenerative disorder may have defective immunomodulatory, tissue protective or reparative capabilities [33]. This possibility has been explored by Mallam et al. [51] and Mazzanti et al. [52], where MSCs from patients with secondary progressive MS (SPMS) and RRMS were found to be broadly similar to controls in a number of parameters. However, Mazzanti et al. found that MSCs of MS patients had significantly greater lipopolysaccharide-stimulated IP10 production compared with healthy controls, while Mallam et al. only explored a relatively small number of patients with MS. In an interesting study, MSC gene expression profiles, as well as function, were compared between control patients and individuals with MS both before and after autologous HSCT. Pre-HSCT, MSCs had distinct transcriptional profiles compared with controls, including downregulation of *TGFB1* and *HGF* genes, and reduced secretion of interleukin (IL)-10 and transforming growth factor (TGF)-B. Six months after transplantation, the transcriptional profile remained similar to pre-transplant AHSCT; post-transplantation, MSCs of MS patients were closer to pre-AHSCT samples than to healthy MSCs. These findings therefore showed that MS MSCs exhibited phenotypic changes, distinct transcriptional profiles and functional defects in immunomodulatory and immunosuppressive activity not 'corrected' by HSCT. This might imply that allogeneic bone marrow MSCs would be better as a putative treatment cell type [53]. However, the question is not definitively resolved, and studies of the phenotype and function of MSCs isolated from MS patients, including those involved in ongoing and planned treatment trials, will be important to explore this issue further [33].

Human bone marrow-derived MSCs can be safely extracted, expanded in vitro and, despite the theoretical risk, do not seem to be susceptible to malignant transformation; thus, they appear to be suitable for clinical application [54]. To date, the largest studies of therapeutic MSC transplantation have been in haematological malignancy, breast cancer, ischaemic heart disease, and graft-versus-host disease [55]. With no induction or conditioning, trials involving MSCs have no treatment-related mortality, and the side-effect profile includes mostly transient and self-

limiting adverse events. This likely safety and the beneficial effects of MSCs in other disorders in these trials (although variable), combined with the experimental indications of likely benefit in whole animal or cellular models, have provided justification for clinical testing in MS. Initially, clinical trials focused on safety and proof-of-concept. In 2008–2009, Connick et al. recruited ten participants with MS, as well as additional controls, and successfully isolated, expanded and characterised MSCs in vitro. This lead to an open-label safety and feasibility trial [7]. An improvement in visual function was reported, as had earlier been suggested in a comparable study by Yamout et al. [56]. Other similarly small trials have reported stabilisation of progression or a modest improvement in the Expanded Disability Status Score (EDSS) with MSC infusion (see Table 1B). An international multicentre trial, MESEMS (Mesenchymal Stem Cells for Multiple Sclerosis) is currently ongoing [57].

At the same time, refinements of the MSC approach are already under experimental consideration. These include priming cells in various ways in culture before infusion, or genetically modifying MSCs in order to putatively improve aspects of their function, including survival, neuroprotective or restorative function, or homing to specific target tissues. One example would be to increase the expression of hepatocyte growth factor, which has been implicated in the efficacy of MSCs in EAE [48].

2.3.1 Related Approaches

MSCs can be obtained from tissues other than the bone marrow. 'PDA-001' is a preparation of mesenchymal-like cells derived from full-term human placenta tissue. It caused a dose-dependent protection from EAE induction and, in established EAE, a reduction of disease progression and severity [58]. PDA-001 has now also been investigated in a multicentre, randomised, double-blinded trial in patients with RRMS and SPMS [59], the first therapeutic trial of its kind to investigate the human placenta as a source for therapeutic stem cells (Table 1). In this study, 81% of patients were taking at least one other licensed MS medication concomitantly, therefore identifying treatment effect was complicated, but PDA-001 administration in patients with MS appeared to be both safe and feasible. PDA-001 may have significant benefits as an alternative source of cells; the full-term placenta is a plentiful source of non-embryonic cells, and production scalability is also feasible [59].

Within bone marrow, a number of stem cell subpopulations are present in addition to HSCs and MSCs, including multipotent adult progenitor cells and STRO-1-positive cells, both of which have been reported to have reparative and neuroprotective properties (as have HSCs). It is suggested that these various populations may contribute synergistically to promote tissue repair (3). Certainly, no one subpopulation has been shown to be more effective than other subpopulations, and some studies report that the unselected (and unexpanded) mixed bone marrow mononuclear cell populations containing all these cell types, and others, may be more effective therapeutically than purified and expanded MSCs. The approach of utilising a filtered preparation of whole bone marrow, aiming to maximise the likelihood of including any and all subpopulations of potentially useful bone marrow-resident stem cells, has been clinically explored in a number of disorders with apparent benefit. We have studied this approach in a small number of MS patients in an uncontrolled phase I trial [60]. Our data support the safety and feasibility of the approach, as well as raising the possibility of a treatment effect. This therapeutic approach, were it to prove beneficial in larger controlled studies [61], would carry the additional advantage of practical ease of adoption and application in non-specialist units, lacking as it does in the cell expansion-related requirement for a Good Manufacturing Practice (GMP) cell culture and selection facility.

Neural stem or precursor cells (NPCs) also have neuroprotective properties, as shown in EAE models, where NPC transplantation can lead to significant reduction of the clinical severity of the disease and reduction of pathological parameters of inflammation [62]. Using a viral model of demyelinating disease, intraspinal transplantation of human embryonic stem cell-derived NPCs resulted in sustained clinical recovery [63]. Recently, a pilot study injecting neural progenitors derived from bone marrow MSCs intrathecally in six patients with MS reported both the safety and feasibility of this approach [95].

3 Efficacy and Safety of Trials in Cell Therapy

Table 1 shows an overview of reported trials of different types of cell therapy in MS. The great majority of these (Table 1A) have explored AHSCT with a mixed cohort of patients with MS, including those with RRMS or SPMS; therefore, distinguishing between efficacy for RRMS and SPMS can be challenging. Nonetheless, given the likely substantial differences in mechanisms of tissue damage and clinical impact, it is worth attempting to interrogate the clinical trial data specifically for distinct effects on relapse activity and progressive disease.

3.1 Efficacy—Relapse Suppression

Individual early case reports showed that treating patients with RRMS using AHSCT was beneficial, particularly in cases with highly active inflammatory disease. These

Table 1 Overview of clinical trials of cell therapy in MS

Author	Time frame	Type of MS (no. of patients or %)	Age, years	Follow-up, years (mean/median)	Treatment	Outcomes	Adverse events (no. of patients or %)
Part A: summary of HSCT/BMT trials							
Fassas et al. [73]	1995–2001	SPMS (19) PRMS (4) RRMS (1) PPMS (11)	Median 40 Range 9–54	11.3	Cy + G-CSF, BEAM or busulfan + ATG, IV PBSC	EDSS improved in 46% 11.3-year PFS 25% Gd+ lesions reduced from 9.53 to 0.17 cm^3	TRM (2)—aspergillosis and pulmonary haemorrhage
Nash et al. [68]	1998–2001	PPMS (8) SPMS (17) RRMS (1)	Median 41	2	Cy + G-CSF, TBI + ATG, IV PBSC	Progression estimate 3 years 27% Gd+ lesion volume decrease 6.6% (1 year)	TRM (1)—EBV PTLD Engraftment syndrome (13/18), MS flare (1), irreversible neurological deterioration (1), UTI (8), bacteraemia (4), central venous catheter infection (1), viral self-limiting illness (7), ITP (1), brachial neuritis (1)
Mancardi et al. [18]	1998	SPMS (10)	Median 35.5 Range 26–52	1.25	Cy + G-CSF, BEAM, IV PBSC	No new T2 lesions in 9/10 EDSS stable/improved	No TRM Febrile neutropenia (9), transient elevation of liver enzymes (2), rash (1), UTI (3), non- or symptomatic CMV reactivation (3), gastric pain (1), subclavian phlebitis (1), SIADH (1)
Capello et al. [82]	1998	RRMS (4) SPMS (17)	Median 24	2	Cy + G-CSF, BEAM + ATG, IV PBSC	EDSS stable or improved 95%	Haemorrhagic cystitis (1), subclavian phlebitis (1), transient SIADH (1), CMV reactivation (6)
Saccardi et al. [83]	1998–2003	SPMS (15) RRMS (4)	Median 36 Range 26–52	3	Cy + G-CSF, BEAM + ATG, IV PBSC	Gd+ suppression 95% 6-year PFS 95% 4.5-year DFS 64%	No TRM Fever (16), haemorrhagic cystitis (1), UTI (1), CVC-related phlebitis (1), inappropriate secretion of ADH (1), sepsis (5), enteritis (1), transient elevation of LFTs (1), gastric ulcer bleeding (1), HZV infection (1), transient monoclonal gammopathy (1)
Kozak et al. [84]	1998–1999	SPMS (11)	Range 25–44	0.71	Cy + G-CSF, BEAM ± ATG, IV PBSC	EDSS improvement 91% Gd+ suppression 55%	No TRM Febrile neutropenia (all), Gram-positive bacteraemia (2), arm cellulitis (1), herpes zoster (1)
Fassas et al. [4]	2000	PPMS (26%) SPMS (70%) RRMS (4%)	Median 39 Range 20–58	1.3	Cy±G-CSF, BEAM, Cy±ATG or TBI and busulphan, IV PBSC and BM	EDSS improvement by ≥1 in 21% at 3 years PFS 74% Disease progression in 20% Gd+ lesions in 33% pre-transplant to 8% post-transplant	TRM-7 patients (5 cytotoxicity, 2 neurological complication) Neurological deterioration (27%), infection/allergic events/severe G-CSF-induced bone pain (15%), infection/cardiac and hepatic toxicity, bleeding, TTP (59%)
Shevchenko et al. [16]	1999–2006	SPMS (27) PRMS (1) PPMS (11) RRMS (11)	Median 32 Range 18–51	1.6	Cy + G-CSF BEAM+ATG, IV PBSC	EDSS improvement in 56% at 6 months No new Gd+ lesions in those without progression 6-year PFS 72%	No TRM Neutropenic fever (51.6%), hepatic toxicity (48.1%), transient neurological dysfunction (22.2%), enteropathy (18.5%), sepsis (2%)
Krasulova et al. [76]	1999–2008	RRMS (11) SPMS (15)	Median 33	5.5	Cy + G-CSF, BEAM+ T-cell depletion, IV PBSC	PFS estimate 70.8% at 3 years, 29.2% at 6 years	No TRM Febrile neutropenia (14), sepsis (11), UTI (7), diarrhoea (16), mucositis (11), arthralgia (1), HSV1 and VZV (1), chronic hepatitis B (1), GBM (1), Acquired anti-factor VIII inhibitor (1)
Ni et al. [69]	2000–2005	SPMS (16) PPMS (2) PRMS (2) Malignant MS (1)	Median 37 Range 15–58	3.5	Cy + G-CSF, TBI or BEAM + ATG, IV PBSC	3.5-year PFS 75% 3.5-year DFS 33.3% Gd+ lesions post-transplant in 14.3% cf 38% at baseline	Non-TRM (2)—severe pneumonia and varicella-zoster virus hepatitis Allergy (2), infection (8), elevation of liver enzymes (6), transient neurological deterioration (5), depression (5)

Table 1 continued

Author	Time frame	Type of MS (no. of patients or %)	Age, years	Follow-up, years (mean/median)	Treatment	Outcomes	Adverse events (no. of patients or %)
Chen et al. [14]	2000–2007	SPMS (19) PPMS (1) RRMS (3) PRMS (2)	Median 37.3 Range 15–64	4.9	Cy + G-CSF, BEAM + ATG, IV autologous PBSC	EDSS 8.0 to 5.5–7.0 (1 year) 3-year PFS 74% Gd+ lesions suppressed/nil new 58%	Non-TRM (2)—pneumonia (1), VZV hepatitis (1) Bacterial infection (13)
Openshaw et al. [24]	2000	SPMS (5)	Range 39-47	2	G-CSF, busulfan + Cy + ATG, IV PBSC	2-year EDSS improvement 50% of survivors Gd+ suppression 100%	TRM (1)—influenza A pneumonia Line infection (1), *C. difficile* diarrhoea (1), severe MS flare (1)—NTRM (1)- *S. pneumonia* sepsis
Hamerschlak et al. [78]	2001–2006	PPMS (4) SPMS (33) RRMS (4)	Mean 42 Range 27–53	1.5	Cy + G-CSF then BEAM/ATG (horse) or Cy/ATG (rabbit), IV PBSC	EDSS improved 63.2% (no difference between two regimens) No new Gd+ lesions	TRM, (3) in BEAM/ATG group—cardiac toxicity/sepsis/alveolar haemorrhage) Febrile neutropenia (18), pneumonia (8), allergy to ATG (5), UTI (7), DVT and PE (3), depression (3)
Atkins et al. [71]	2001–2009	RRMS (12) SPMS (12)	Median 34 Range 24–45	6.7	Cy+G-CSF, busulfan, Cy+ATG, IV PBSC	3-year DFS 69.6% No new Gd+ lesions	TRM (1) – hepatic necrosis UTI (13%), ITU admission (sinusoid obstruction syndrome), febrile neutropenia (all), positive cultures (29), viral infections (26%), thyroid dysfunction (5), immune thrombocytopenia (1)
Burt et al. [85]	2003	RRMS (21)	Range 21–52	2.6	G-CSF + Cy, IV PBSC	EDSS $\leq$6.0 stable 43% Gd+ suppression 57%	Non-TRM (2) – Pseudomonas bacteraemia (1), dermatomal zoster (2), disseminated zoster (1), rash/fever/fatigue (5)
Burt et al. [75]	2003–2005	RRMS (21)	Median 33 Range 20–53	3.1	Cy + G-CSF, Cy+ alemtumuzab/ATG, IV PBSC	EDSS improvement 1 point 81% 3-year RFS 76% 3-year DFS 62%	No TRM *C. difficile* diarrhoea (1), dermatomal zoster (2), ITP (2), neutropenic fever (5), transient neurological hypoaesthesia (1)
Burt et al. [70]	2003–2014	RRMS (123) SPMS (28)	Mean 36 Range 18–60	2.5	Cy + G-CSF, alemtuzumab/ATG, IV autologous PBSC	EDSS 4.0–2.5 (4 years) 4-year RFS 80% 4-year PFS 87% T2 lesion volume 8.57–5.74 cm^3 (27 months)	No TRM Dermatomal zoster (4), ITP (7), hypothyroidism (7)
Saiz et al. [86]	2004	SPMS (9) RRMS (5)	Median 30 Range 22–45	3	Cy + G-CSF, BEAM+ ATG, IV PBSC	3-year PFS 85.7% 3-year DFS 46.4% No new T1 lesions 50% reduction in T2 lesion volume	No TRM Neurological deterioration (3), secondary amenorrhoea (4)
Fagius et al. [67]	2004	RRMS (9)	Median 27 Range 9–34	2.4	Cy + G-CSF, BEAM+ ATG, IV PBSC	Median EDSS improvement 3.5 No new T2 lesions	No TRM Crohn's disease (1) Mucositis, alopecia, sepsis (2), serum sickness (2), herpes zoster (1)
Mancardi et al. [80]	2004–2009	SPMS (6) RRMS (7) PRMS (8)	Mean 36 Range 22–46	4	Cy + G-CSF, BEAM+ ATG and IV PBSC, compared with MTX	AHSCT reduced number of T2 lesions by 79% compared with MTX No difference noted in the progression of disability	No TRM Febrile neutropenia/diarrhoea/leukopenia/mucositis/anaemia/amenorrhoea, reduced platelet count (80%) Prolonged hospitalisation with late engraftment (1), systemic candidiasis and CMV reaction (1), ATG reaction (1)

Table 1 continued

Author	Time frame	Type of MS (no. of patients or %)	Age, years	Follow-up, years (mean/median)	Treatment	Outcomes	Adverse events (no. of patients or %)
Bowen et al. [87]	2005–2008	SPMS (17) PPMS (8) RRMS (1)	Median 41 Range 27–60	4	TBI, Cy + ATG, IV PBSC	EDSS improved 15% 3-year PFS 63% 6-year PFS 48% New MRI lesoins in 4 patients	TRM – EBV PTLD (1) NTRM (4) Myelodysplastic syndrome (1) (post 7 years Tx with mitoxantrone)
Shevchenko et al. [88]	2005–2011	RRMS (43) SPMS (56)	Mean 35	4	BEAM-like conditioning, G-CSF, IV PBSC	8-year disease progression 16.7% Event-free survival 80%	No TRM
Shevchenko et al. [23]	2006–2011	SPMS (35) PPMS (15) PRMS (3) RRMS (42)	Mean 34.5	3.8	G-CSF, BCNU/CCNU and melphalan/mini-BEAM-like + ATG, IV PBSC	EDSS improvement or stabilisation 80% 5-year PFS 92% (early AHSCT), 73% for conventional salvage AHSCT	No TRM Thrombocytopenia (100%), neutropenia (100%), fatigue (100%), anaemia (80%), alopecia (80%), hepatic toxicity (42.1%), transient neurological decline (27.4%), enteropathy (7.4%), skin allergy (8.4%), pneumonia (2.1%), uterine bleeding (2.1%), oral herpes (1.05%), genital herpes (1.05%), sepsis (3.2%)
Xu et al. [89]	2001–2006	SPMS (22)	Median 35.5 Range 20–51	3.25	G-CSF, BEAM, IV PBSC	3.25-year PFS 77% 59% of patients had neurological improvement	No TRM Diarrhoea (13), fever (6), transient neurological decline (8), bacterial infection (7)
Samijn et al. [90]	2006	SPMS (14)	Median 35 Range 23–50	3	Cy, TBI + ATG, IV BMSC	EDSS improved 14% 3-year PFS 36% No new Gd+ lesions	No TRM Mucositis (10), rash (6), alopecia (all), fatigue (all), *C. difficile* diarrhoea (2), fever (all), EBV PTLD (1), antithyroid antibodies (3), myelodysplastic syndrome (1), herpes zoster (1), neurological deterioration (2), muscle spasms (2), loss of visual acuity (3)
Rocca et al. [28]	2007	SPMS (14)	Mean 38 Range 23–50	3	ATG + Cy, TBI, IV PBSC	Gd+ suppression 100% Stabilisation or improvement in EDSS in 35.7%	No TRM EBV PTLD (1), antithyroid antibodies (3), myelodysplastic syndrome (1)
Burman et al. [72]	2014	RRMS (40) SPMS (2) PPMS (2)	Mean 31 Range 9–52	3.9	Cy + GC-CSF, BEAM + ATG or Cy/ATG, IV PBSC	5-year RFS 87% MRI event-free survival 85% 5-year PFS 77% 5-year DFS 68%	No TRM Herpes zoster reactivation (17%), thyroid disease (8.3%), *C. diff* (4.2%), neutropenia fever (35), invasive fungal infection (2.1%), Crohn's disease (1), alopecia areata (1), epilepsy (1)

Author	Time frame	Type of MS (no. of patients)	Age, years	Follow-up (mean/median)	Treatment	Outcomes	Adverse events (no. of patients)
Part B: summary of MSC/related trials							
Rice et al. [60]	2007–2009	RPMS (6)	Mean 47.7	12 m	IV (BM) mononuclear preparation	Multi-modal evoked potentials showed significant neurophysiological improvement	Transient increase in lower limb spasticity (2), urinary retention (1)
Connick et al. [7]	2007–2010	SPMS (10)	Mean 48.8 Range 40–53	5.8–10.2 m (mean 7.0 m)	IV (BM) autologous MSC	Improvement in visual acuity and visual evoked response latency Increase in optic nerve area	Rash following infusion (all), bacterial infection (2)
Llufriu et al. [91]	2010–2012	RRMS (5)	Median 41 Range 23–48	12 m	IV (BM) autologous MSCs	Gd+ lesions at 6 months reduced (12.3 to 3.1)	Upper respiratory infection (1), influenza (1), gastroenteritis (1), herpes labialis (1)
Karussis et al. [41]	2010	RR or progressive MS unresponsive to treatment (15)	Mean 35.3 Range 27–60	6 m	IT (+IV in 5) autologous BM MSCs	EDSS 6.7 to 5.9 No new Gd+ lesions at 6 months	Transient fever (10), headache (10), meningeal irritation and aseptic meningitis (1)

Table 1 continued

Author	Time frame	Type of MS (no. of patients)	Age, years	Follow-up (mean/median)	Treatment	Outcomes	Adverse events (no. of patients)
Yamout et al. [56]	2010	SPMS (7)	Range 34–56	12 m	IT + intracisternal autologous BM MSCs	Vision and low contrast sensitivity at 3 months improved in 83% Some MRI deterioration	Transient encephalopathy (1), cervical and back pain (1)
Bonab et al. [92]	2008–2010	SPMS (23) PRMS (2)	Mean 34.7	12 m	IT (BM) autologous MSCs	EDSS 6.1 to 6.3 (1 year)	Low-grade fever (all), nausea-vomiting (2), weakness in lower limbs (2) and headache (3)
Lublin et al. [59]	2010–2011	RRMS (7) SPMS (5)	Low-dose median 52.5, high-dose median 47.5	12 m	IV human placenta tissue (non-autologous), PDA-001 (mesenchymal-like stem cells)	No significant change in EDSS or Gd+ lesions	MS flare (6%), anaphylactoid reaction (6%), superficial thrombophlebitis (6%), headache (44%), URTI (31%), fatigue (25%), infusion site reactions/events (4) and UTI (25%)
Li et al. [93]	2010–2012	RRMS+SPMS (13) Placebo (10)	Mean 41.7	12 m	IV non-autologous human umbilical cord-derived MSCs	EDSS score and relapse recurrence significantly lower than the control group	None reported
Cohen et al. [94]	2014	RRMS (10) SPMS (14)	Mean 46.5	6 m	IV autologous MSCs with human fibroblast growth factor 2	No significant improvement noted	No serious AE reported

Unless otherwise stated, clinical outcome data are stated for the end of the follow-up period

ADH antidiuretic hormone, *AE* adverse event, *AHSCT* autologous haematopoetic stem cell transplantation, *ATG* antithymocyte globulin, *BCNU* carmustine, *BEAM* carmustine, etoposide, cytosine-arabinoside, melphalan, *BM* bone marrow, *BMSC* bone marrow-derived stem cells, *BMT* bone marrow transplant, *CCNU* lomustine, *CMV* cytomegalovirus, *CVC* central venous catheter, *Cy* cyclophosphamide, *DFS* disease activity-free survival, *DVT* deep vein thrombosis, *EBV PTLD* Epstein–Barr virus post-transplant lymphoproliferative disorder, *EDSS* Extended Disability Status Score, *GBM* glioblastoma multiforme, *G-CSF* granulocyte colony-stimulating factor, *Gd+* gadolinium-enhancing magnetic resonance imaging lesions, *HSCT* haematopoietic stem cell transplantation, *HSV1* herpes simplex virus type 1, *HZV* herpes zoster virus, *IT* intrathecal, *ITP* idiopathic thrombocytopenic purpura, *ITU* intensive therapy unit, *IV* intravenous, *LFTs* liver function tests, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *MSC* mesenchymal stromal cells, *MTX* mitoxantrone, *PBSC* peripheral blood stem cells, *PE* pulmonary embolism, *PFS* progression-free survival, *PPMS* primary progressive MS, *PRMS* progressive-relapsing MS, *RFS* relapse-free survival, *RRMS* relapsing-remitting MS, *SIADH* Syndrome of Inappropriate Antidiuretic Hormone, *SPMS* secondary progressive MS, *TBI* total body irradiation, *TRM* transplant-related mortality, *TTP* thrombotic thrombocytopenic purpura, *Tx* treatment, *URTI* upper respiratory tract infection, *UTI* urinary tract infection, *VZV* varicella zoster virus

patients showed significant suppression of relapses over a period of 12–24 months, without any additional disease-modifying therapies (DMT). MRI findings also suggested no subclinical disease activity. These examples demonstrated the therapeutic potential of AHSCT [64, 65]. Another case report explored the administration of cyclophosphamide and non-myeloablative AHSCT (and ATG) in a patient with malignant-type MS, with a pre-treatment EDSS of 8.0, which improved to 6.5 after 1 year, with no new lesions demonstrated on MRI [66], again suggesting that AHSCT can be effective and safe even during periods of extreme inflammation and disability, with a lasting therapeutic effect. Similar dramatic improvements in EDSS with suppression of relapse activity were noted in other patients with 'malignant' RRMS [67]. However, recurrence of relapse after autologous HSCT can occur and has been attributed to both the pre-transplantation conditioning regimen (failing to eliminate all antimyelin reactive cells) [68] and T lymphocytes that may be present among the autologous graft [69].

Following these earlier reports, Burt et al. [70], utilising a non-myeloablative AHSCT approach in a relatively large study (123 patients with RRMS and 28 patients with SPMS), showed impressive outcomes, with 80% of patients showing relapse-free survival at 4 years. The adverse event profile was good, with a few cases of idiopathic thrombocytopenic purpura and autoimmune thyroid disorder, and no TRM. It is worth noting that during the conditioning period, alemtuzumab was utilised, and since this immunomodulatory drug is highly effective in RRMS, it is difficult theoretically to isolate the specific benefit of AHSCT.

Using a more aggressive immune ablative approach, Atkins et al. [71] recently reported dramatic relapse activity effects, with not a single relapse occurring in 24 patients post-AHSCT and not a single gadolinium-enhancing lesion on repeated post-transplant MRI scanning. However, there were a number of adverse events, including hepatic necrosis (resulting in death), an intensive therapy unit (ITU) admission involving sinusoid obstruction syndrome, thyroid dysfunction, and febrile events including positive cultures. Others have reported marked beneficial effects in active RRMS sustained at 5 years [96].

3.2 Efficacy—Preventing Disability Progression

Here, efficacy is often expressed as progression-free survival (PFS), defined as the absence of a confirmed increase in EDSS by at least 1 point. In studies with a follow-up of at least 2 years, PFS ranged from 36% to 100%, and only a minority of patients showed an improvement in EDSS [22]. There are a number of complications in assessing the clinical significance of such studies. First, disability progression in relatively short-term studies in MS is notoriously unreliable, partly because progression is often very slow in MS and partly because disability changes in relatively short-term studies may substantially reflect improvement from pre-HSCT relapses rather than implying changes in underlying disease progression. Thus, in the study by Burman et al., where improvement was reported, the majority of the improvement took place during the first year, with some additional improvement in the second year, but no further improvement subsequently [72]. In the assessment of effects on disability progression, most authorities lend more weight to longer-term studies, such as Fassas et al. [73]; here, PFS was notably lower than in those studies with shorter-term follow-ups.

Second, often impressive and sustained suppression of Gd+ lesions or overall volume of T2 lesion load reduction on MRI can been noted post-AHSCT [24, 74]. However, perhaps unsurprisingly, these positive MRI findings do not necessarily imply, and have not been accompanied by, comparable improvements in clinical disability in patients. Suppression of MRI enhancement in trials using myeloablative regimens in patients with progressive disease is difficult to interpret as, in the progressive phase of MS, MRI enhancement normally decreases spontaneously over time [75].

Third, the relationship between relapses and disease duration prior to treatment should be considered; relapse frequency decreases with disease duration in MS, and therefore the results of studies assessing disability progression are less likely to be 'contaminated' by relapses (and recovery) if patients with more chronic disease are targeted. Burt et al. found that the EDSS score did not improve in patients with disease duration longer than 10 years [70] (or more generally in patients with SPMS). A related, confusing influence of relapses may explain the results of studies showing that patients with SPMS have a higher probability of remaining 'progression-free' than those with PPMS [68].

In a retrospective survey of the EBMT database, the advantages of treating early in the inflammatory phase of the disease were discussed; younger patients transplanted within 5 years from diagnosis showed significantly better PFS [19]. Similarly, Krasulova et al. commented that patients with relapsing MS, disease duration <5 years and age <35 years have a more favourable outcome from AHSCT [76]. MS patients with long-lasting disability have been shown to be poor responders to HSCT, presumably due to the likely irreversibility of chronic lesions [69].

In the study by Burt et al. exploring less intense immunosuppression [70], 87% of patients were found to have PFS. It is worth mentioning that the mean age of patients in this trial was lower and RRMS patients were predominantly recruited. The trial also had a relatively short follow-up period (median follow-up 2 years). Even

with more intense myeloablation, Atkins et al. reported 69.6% of patients to have disease-free survival at 3 years [71].

Recently, 'NEDA' status has gained ground as an outcome measure in MS therapeutics. 'No evidence of disease activity' is defined as an absence of relapse activity, progression and MRI evidence of disease activity (no new or gadolinium-enhancing lesions). Although not yet used prospectively as an outcome measure in BMT trials, retrospective application of NEDA criteria has indicated that, in highly active MS, AHSCT may be superior to current drug treatments in achieving NEDA [97].

3.3 Safety

The majority of trials have explored conditioning regimens utilising BEAM therapy—carmustine (**B**iCNU®), **E**toposide, cytarabine (**A**raC) and **M**elphalan—combined with mobilising procedures that include cyclophosphamide and G-CSF, CD34+ selection and ATG in vivo purging. The various cytotoxic agents involved carry significant potential side effects, and immunoablation naturally also carries significant risks, hence the need to seriously consider the adverse effect profile of AHSCT.

Myeloablative transplant regimens (such as TBI or full-dose busulfan) cause irreversible bone marrow failure, thus absolutely requiring HSC reinfusion to regenerate bone marrow function. Toxicity and late complications can be substantial with myeloablative regimens, as demonstrated in Table 1. TBI is associated with a higher mortality, and it has also been speculated that TBI may induce an endogenous factor that enhances demyelination or interferes with ongoing remyelination [24]. The disadvantage of adding cyclophosphamide to G-CSF is an increased risk to the patient due to an extended pancytopenic interval. There is an increased cost of management of patients receiving chemotherapy, and a delay in proceeding to high-dose immunosuppressive therapy [68]. The study by Fassas et al. [4] had a high mortality but valuably demonstrated that there was no evidence that more intense conditioning, purging or ATG use was associated with higher probabilities of confirmed PFS [4].

The most frequent adverse event noted in AHSCT was febrile neutropenia; however, there is also a high incidence of urinary tract infection, perhaps not unexpected in patients with MS given the frequency of neurological bladder dysfunction, particularly in progressive disease. The increased risk of infections in patients with reduced mobility, together with restrictive pulmonary defects, supports the current suggestion of targeting patients with lower EDSS scores [22]. The most frequent late adverse events reported in MS patients undergoing HSCT are varicella zoster virus and herpes simplex virus reactivation, followed by the development of autoimmune disease, including autoimmune thyroiditis [22].

TRM is clearly the greatest concern, and any risk might be considered too high in relation to a condition such as MS, which is not life-threatening per se [77]. One retrospective survey looked at 183 patients with MS in the database of the EBMT Registry [19]. The overall TRM was 5.3%, but, importantly, this mortality was only noted in the period 1995–2000, with an apparent 0% TRM reported subsequent to the year 2000. In addition, no deaths were noted in those treated with BEAM without graft manipulation. Improvement or stabilisation of the neurological condition was noted in 63% of patients, at a median follow-up of 41.7 months, and was irrespective of the conditioning regimen. The analysis also suggested that in those using a moderate conditioning regimen, a durable benefit was seen in some patients, quoting figures post-HSCT of up to 9 years [19]. These observations provided further impetus for exploring alternative approaches to conditioning, although it should also be stressed that better patient selection criteria and better supportive care, including infection prophylaxis, are also likely to have contributed to the more recent reduction in TRM.

The study by Hamerschlak et al. is the only trial that has directly compared the toxicity of different conditioning regimes [78]—BEAM/ATG (horse) against the cyclophosphamide/ATG (rabbit) regimen. The overall complication rate in the BEAM/ATG group was 71.4%, considerably higher than the cyclophosphamide/ATG group figure of 40%. Three subjects (7.5%) in the BEAM/ATG group died (one each from cardiac toxicity, sepsis and alveolar haemorrhage). Moreover (and as with the retrospective EBMT Registry survey), the efficacy results were broadly similar, although the period of follow-up was relatively short [78].

3.4 Cost and Risk Benefit

Measurement of long-term benefit in MS clinical trials has long been recognised to be extremely challenging. Determination of the risk–benefit ratio is also difficult, especially for early MS patients with mild to moderate disability and low EDSS scores, since the prognosis for long-term survival is good despite worsening physical ability [79]. Six years ago, and in the most optimistic scenario, the cost effectiveness of AHSCT was considered to be approximately £2800 per additional quality-adjusted life-year (QALY) gained [5]. The initial costs of HSCT are extremely high, and for any new and costly treatments to be widely applied in a resource-constrained health service, such as the National Health Service in the UK, as well as many other health services, it is necessary to demonstrate value for money in the context of other competing priorities [5]. At present, no phase III, prospective, randomised

studies have been conducted that compare the efficacy of AHSCT against other conventional therapies. The only comparative trial is the Autologous Haematopoietic Stem Cell Transplantation Trial in MS (ASTIMS), a phase II study designed to assess the effect of AHSCT versus mitoxantrone on disease activity in MS, measured by MRI in the 4 years following treatment [80]. The results of this trial are summarised in Table 1. In terms of cost effectiveness and benefit of AHSCT, and utilising a 6-month sustained progression rule, the study demonstrated that AHSCT is less effective than mitoxantrone, using a decision-analytic Markov model for evaluation [80]. However, mitoxantrone is little used now in MS, diminishing the practical value of this study.

To assess the risk–benefit ratio of HSCT in MS, Daumer et al. investigated the natural history of moderately severe MS, and concluded that the probability of reaching an EDSS score of 10 (death) after 15 years was 22%. In the study by Fassas et al., exploring the long-term outcome of HSCT, the combined disease- and procedure-related mortality was 17%, thus, at face value, comparatively favourable [73, 79]. In the study by Daumer et al., the risk for progression to advanced disability, defined as an EDSS score of 8, was very low for the subgroup with a baseline EDSS score of 3–3.5. However, among those with a baseline EDSS score of 4–5.5, 3% had advanced disability after 2 years, 5% after 3 years, 6% after 4 years, 12% after 5 years, and 40% after 10 years [79]. In light of this, the PFS rates of AHSCT trials might be seen as favourable, although there is little evidence from long-term follow-up studies.

In summary, there are clearly still significant gaps in the evidence, and the next steps would involve exploring phase III randomised trials, with larger recruitment of patients and longer follow-up, and, in particular, comparison against current licensed, more potent treatments, including natalizumab and alemtuzumab, to elicit the true efficacy of cell therapy and to assess the cost effectiveness and risk versus benefit quotient in these patients. Only one trial with considerable follow-up of 11.3 years commented that disease progression (with or without initial improvement post HSCT) still occurred in a significant proportion of their patients despite impressive sustained effect in suppressing activity on MRI, suggesting that HSCT is not a therapy for the progressive population of MS and should be reserved for those with aggressive relapsing disease, in the inflammatory phase, and for the malignant form of MS [67, 73].

4 Conclusions and Future Considerations

Considerable advances in our understanding of MS physiology point to the need for a paradigm shift in the management of MS from one that simply targets CNS inflammation towards one that aims to be both immunomodulatory and neuroprotective, and which additionally carries the potential for regenerative repair. Cell therapies intended to achieve repair by direct cell replacement have made limited progress towards clinical application, largely because of questions concerning the basis of this approach. However, related studies of the cellular biology of remyelination have yielded a number of molecular candidates for more conventional pharmacological approaches to myelin repair.

With regard to HSCT, better outcomes are evident in patients with active inflammatory disease, shorter disease duration and lower EDSS scores, and in those with RRMS rather than SPMS and PPMS. This is consistent with a treatment targeting control of peripheral immunopathology rather than directly affecting pathological processes within the CNS [22]. The increasing experience of neurologists and haematologists with conditioning regimens and myeloablative versus non-myeloablative treatment protocols, as well as in the management of adverse effects, has led to significant reductions in TRM. While the precise place of HSCT in any overall treatment paradigm for MS remains to be defined, it is increasingly no longer seen as a last resort for patients with a poor prognosis [22].

Recent trials are exploiting the immunomodulatory, neuroprotective and reparative properties of other bone marrow-derived stem cells, such as MSCs, and of comparable cells from bone marrow and other sources. These approaches carry a number of practical advantages, including relative ease of access and safety of administration, as well as avoiding the need for immunosuppressive treatment to prevent rejection [41]. Thus far, published trials have been limited to small safety and feasibility studies, and while these have shown a favourable adverse event profile, the efficacy of MSC transplantation has appeared modest. The same applies to trials that have explored the avenue of non-selected, non-expanded cells. Phase II/III trials of both approaches are now underway [57, 61, 81]. With regard to other cell types, such as human placental-derived stem cells, there is even less trial evidence [59].

In an era where cell therapy has been rapidly expanding in other fields such as cardiovascular medicine, and with the limited options of conventional treatments available for progressive MS, there is a drive to accelerate trials in MS to explore the efficacy and cost effectiveness of cell therapy. However, it is only by recruiting patients to carefully designed clinical trials, as well as populating detailed registries, that we will acquire sufficient data to enable us to answer the question of whether cell therapy is truly beneficial to the general population of patients with MS.

Compliance with Ethical Standards

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Conflict of interest Pamela Sarkar, Claire M. Rice, Neil J. Scolding report no relevant conflicts of interest.

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