Systematic Review/Meta-analysis

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Immunological outcomes of autologous hematopoietic stem cell transplantation for multiple sclerosis: a systematic review

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Background: Autologous hematopoietic stem cell transplantation (AHSCT) is an extensive procedure that allows for the depletion of the immune system and its restoration from hemopoietic stem cells. The approach has been modified for the treatment of severe immune-mediated illnesses, including multiple sclerosis (MS), after being initially devised for the treatment of hematological malignancies.
Objective: This systematic review aims to determine and consolidate the information on the short-term and long-term immunological effects of AHSCT on the cellular level in MS patients.
Methods: The PubMed, Scopus, and Web of Science servers were used to conduct a systematic search in compliance with the PRISMA guidelines. The results were tabulated and analyzed.
Results: A total of 17 studies (10 clinical trials, 6 cohort studies, and 1 case–control study) were included in the final analysis, and 383 MS patients were analyzed. A significant decline in the cell count of CD4 T cells was reported when compared to the CD8 T cells, B cells, and NK cells. B cell count returned to baseline in 71.4% of the studies at the end of 6 months. The NK cell count was found to be above the baseline in 62.5% of studies.
Conclusion: AHSCT has been proven to be one of the most effective treatment modalities for MS in recent studies. However, debilitating complications due to immunological outcomes of the procedure have led to increased morbidity. Further research into this domain will help boost the success rate and efficacy of AHSCT.

Keywords autoimmune disorders, autologous hemopoietic stem cell transplant, immune cells, multiple sclerosis, myeloablation

Introduction

Multiple sclerosis (MS) is a chronic neurological disorder that affects the central nervous system (CNS). It is a complex and often debilitating condition that can significantly impact a person's quality of life and poses numerous challenges for both patients and healthcare providers. Its unpredictable course causes symptoms and signs because of the involvement of motor, sensory, visual, and autonomic systems[1]. It is characterized as an organ-specific T-cell-mediated autoimmune disease. It is a two-stage disease, early relapsing–remitting disease and delayed non-relapsing progression.

MS can manifest in various forms, each presenting distinct clinical features and disease courses. The most common types include relapsing–remitting multiple sclerosis (RRMS), secondary-progressive multiple sclerosis (SPMS), primary-progressive multiple sclerosis (PPMS), and progressive-relapsing multiple sclerosis (PRMS)[2]. Each type has its unique progression pattern, with some characterized by periodic relapses and remissions, while others show a steady decline over time.

The pathogenesis of MS involves a complex interplay between the immune system, the CNS, and various cellular and molecular

HIGHLIGHTS

- The current study is an overview of autologous hemopoietic stem cell transplant as a treatment modality in multiple sclerosis (MS).
- This systematic review analyzes immune reconstitution post autologous hemopoietic stem cell transplant in patients with MS.
- This review highlights the average time taken by each immune cell to return to baseline after a stem cell transplant.

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mechanisms. The immune cells, particularly T and B cells, play a significant role in initiating the inflammatory response and attacking the myelin sheath[3.] The presence of oligoclonal bands in the cerebrospinal fluid further suggests the immune system's involvement in MS. The resulting inflammation triggers a cascade of events, including demyelination, axonal damage, and scar tissue (sclerosis) formation, which collectively contribute to the clinical manifestations of MS. However, the exact cause of MS remains unclear, and it is believed to involve a combination of genetic, environmental, and immunological factors.

A way of measuring disability in MS and tracking changes in the degree of disability over time is the Expanded Disability Status Scale (EDSS) of Kurtzke, which is frequently used for the evaluation of MS patients[4].

Numerous advancements in the field of MS treatment are being tried that are improving the outcomes in patients with MS, but the disease remains incurable[5.] Treatments for MS attacks include corticosteroids and plasma exchange; disease-modifying therapies (DMTs) are essential for slowing down and modifying the disease progression. High-efficacy monoclonal antibody (mAb) DMTs are frequently regarded as first-line MS treatment options; however, further study is required to determine the optimum DMT sequencing techniques[6.] Mitsikostas and Goodin concluded that IFNβ-1b or IFNβ-1a administered subcutaneously several times per week and glatiramer acetate (GA) are roughly equivalent in terms of efficacy measured by relapsing rate and EDSS and that both these medications and many other DMTs are superior to weekly intramuscular IFNβ-1a[7].

The recent intervention in this discipline is autologous hematopoietic stem cell transplantation (AHSCT). Recent trials on AHSCT showed that it was more effective than DMTs at slowing the disease's progression. The current study's objective is to present a comprehensive analysis of how AHSCT affects B cells, T cells, and NK cells. The review also enhances doctors' understanding of the difficulties resulting from immunologic outcomes and steps that can be taken to avoid them.

Methods

The systematic review was done according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Supplemental Digital Content 1, http://links.lww.com/MS9/A304) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) guidelines (Supplemental Digital Content 2, http://links.lww.com/MS9/A305). The review was registered on PROSPERO (ID: CRD42023432337).

Data sources and search strategy

A comprehensive search was conducted in PubMed, Scopus, and Web of Science databases without publication period restriction. The keywords used are summarized in Table 1. The search process was completed separately by two researchers. The studies' significance level was further screened by appropriately evaluating the publications' titles, abstracts, and full text. A total of 17 articles were included and reviewed.

Table 1

Keywords used for searching data sources.

Disease terms	"Multiple sclerosis" AND/OR "Relapsing-remitting multiple sclerosis" AND/OR "Relapsing multiple sclerosis"
Treatment terms	"Autologous hemopoietic stem cell transplant" OR "Autologous stem cell transplant"
Immunological terms	Lymphocyte OR leukocytes OR ("B cell" or "B lymphocyte" OR "B memory" OR "naive B") OR ("T cell" OR "T lymphocyte" OR "T memory" OR "T regulatory" OR "T helper" OR "naive T") OR ("natural killer" OR "NK cell")

Eligibility criteria

The studies were included or excluded as per the defined inclusion and exclusion criteria. Randomized control trials (RCTs), cohort studies, case–control studies, and other original research articles on autologous hematopoietic stem cell transplants in MS patients were included in the study. We considered the following exclusion criteria:

(1) Non-original studies, including conference abstracts, review articles, protocols, case reports, animal studies, and editorials.
(2) Articles in a language other than English.
(3) Lack of distinct data regarding the immune cell population after AHSCT.
(4) Unavailability of full texts.
(5) Trials on patients with other conditions.

Study selection

RevMan software was used to organize the search results and remove duplicates. Eight authors independently screened 377 non-duplicated records, and the conflicts were resolved after a discussion with D.A., S.S.M., and Y.I. A total of 153 articles were excluded in the first round of screening for being out of the scope of the current study, conference abstracts, review articles, or in a language other than English. In the second round of screening, 206 articles were excluded due to a lack of specific data about immune cells, not including MS patients and animal studies.

Data extraction

Required data were extracted by eight authors of the research team as follows: first author name, year of the study, place of study, number of subjects and controls, mean age, gender, disease type, mean disease duration, and immune cell changes. The results of the included articles are discussed in Table 2. The first author investigated the extracted data and settled any disagreements among the other authors.

Quality assessment

Newcastle–Ottawa Scale (NOS) for cohort and case–control studies was implemented to critically appraise the included studies (Supplemental Digital Content 3, http://links.lww.com/MS9/A306). The jaded scale was used for RCTs. The risk of bias was assessed by eight authors independently. The risk of bias analysis is made available in the Supplementary Material (Supplemental Digital Content 4, http://links.lww.com/MS9/A307).

Statistical analysis

All data were extracted onto a predesigned Excel sheet and represented in percentages, mean, and standard deviation for appropriate variables.

Results

A total of 17 studies (10 clinical trials, 6 cohort studies, and 1 case–control study) were included in the final analysis. Data from the included studies are presented in Table 2. The selection process for articles is shown in the PRISMA diagram (Fig. 1).

Patient characteristics

The review included a total of 383 participants, out of whom 59% ($n=226$) were women and 41% ($n=157$) were men, with a mean age of 36.98 years. The mean disease duration is 8.63 years. Of the 17 studies, 70.58% ($n=12$) of studies included RRMS patients, 58.82% ($n=10$) included SPMS patients, 29.41% ($n=5$) included PPMS patients, and one study included PRMS patients.

Conditioning regimen

About 70.5% ($n=12$) of the studies used a myeloablative conditioning regimen, which constituted the BEAM protocol [dichloro-ethyl-nitrosourea (BCNU) 300 mg/m^2, cytosine arabinoside 200/800 mg/m^2, etoposide 200/800 mg/m^2, and melphalan 140 mg/m^2 associated with antithymocyte globulin (ATG)] and 29.5% ($n=5$) of the studies reported the use of non-myeloablative conditioning regimens, which included Cy 200 mg/m^2 and ATG.

T lymphocytes

Two articles that analyzed the total T-cell count revealed a drop in one while maintaining the count in the other. Five articles discussed T regulatory cell trends, of which three studies (60%) showed an increase above baseline and two studies (40%) showed a return to baseline at the end of 6 months of the follow-up period. On the contrary, out of the 15 studies that reported total CD4 cells, four studies observed a return to the baseline over 1–3 years, while 73.33% reported a decline below the baseline. The trends in CD4 naive cells followed a similar pattern, with four out of six studies (66.66%) reporting a decline in cell count below the baseline, while the other articles reported a return to baseline in one and an increase over the baseline in another. The trends in CD4 memory cells took a comparable course, where central memory cells reported a decrease below the baseline in all the studies ($n=4$), while effector memory cells reported a decline in 75% of articles. The CD4 effector cell count was reported in two articles and it returned to baseline. The trends in CD8 cells varied highly compared to CD4 cells. Total CD8 cell count increased in 40% of studies ($n=4$) and decreased in 30% of studies. CD8 naive cells returned to baseline in 57.14% of articles ($n=4$), while decreasing in 42.85% of articles; 50% ($n=2$) of the articles reporting CD8 central memory cell count reported a decrease below the baseline, while 75% ($n=3$) of the articles reported an increase above the baseline. CD8 effector cells were analyzed in two articles and returned to baseline in both of them. Table 3 describes the trends of each immune cell at the end of 2–6 months, 1 year, and 2 years.

B lymphocytes

Total B cell count was studied in six articles, among which 50% ($n=3$) of articles reported a return to baseline, 33.33% reported an increase above the baseline, and the count was maintained in another article. Memory B cell was analyzed in three studies, and it remained below the baseline in all of them. Trends in plasma cells followed a similar course, where all three articles (100%) reported a decline below the baseline. Three studies ($n=3$, 42.8%) reported on naive B cells, of which counts grew and remained above baseline in two studies, and declined, then increased but remained below baseline in one study.

NK cells

The trends in NK cells were contrary to those observed in T cells and B cells. Nine articles studied the effect on NK cells. One article reported a decline in the count but eventually reached the baseline. The counts increased in seven articles ($n=7$, 77.78%) out of which three articles were reported to remain above the baseline ($n=3$, 42.85%), and three articles returned to the baseline ($n=3$, 42.85%) over 1–3 years' time period. The counts were maintained in one article.

Discussion

AHSCT involves the ablation and reconstitution of the immune system to eliminate malignant cells or treat autoimmune diseases[25]. This treatment offers various advantages as it improves bone marrow activity and possesses no risk of graft versus host disease. It produces functional cells to replace malfunctioning cells in immune deficiency syndromes, and other illnesses[26]. AHSCT has been proven to be safer over time, and its application has expanded to non-malignant disorders such as autoimmune disease[27]. The ablation is carried out by various myeloablative and lymphoablative regimens. However, as lymphoablative regimens have replaced myeloablative techniques more frequently throughout time, the safety of AHSCT has significantly increased. Lymphoablation is thought to destroy lymphocytes and lymphoid progenitors more selectively than myeloablation, thus lowering the irreversible toxicity to the bone marrow. As a result, it seems to facilitate a quicker recovery while minimizing the likelihood of hematologic immune challenges[28].

The sources of hematopoietic stem cells are the bone marrow or the peripheral blood, which can be cryopreserved. Currently, peripheral blood stem cells are the most widely used method for AHSCT[29]. Peripheral blood stem cells are extracted by leukapheresis following mobilization, where the granulocyte colony-stimulating factor is used to mobilize CD34 + stem cells from the bone marrow into the peripheral circulation. The most often used medication for mobilization is cyclophosphamide[30]. Before stem cell infusion, a high-dose immunosuppressive treatment, which includes chemotherapy and therapeutic antibodies, is delivered (conditioning phase). Stem cell infusion is followed by the aplastic phase where the immunological and hematopoietic mechanisms are unable to produce enough cells to sustain blood counts and innate immunity. The balance of antibiotic transfusions, symptomatic treatment, and constant monitoring is necessary for effective treatment of the patient. Ultimately, this is followed by the stage of engraftment, in which the infused hematopoietic stem cells divide to produce mature cells in the blood[31].

Table 2

Table representing the data extracted from the articles.

First author	Year of study	Study design	Place of study	Intervention (N)	Comparator (N)	Disease type	Mean age (years)	Gender	Mean disease duration years	Conditioning regimen	T cells	B cells	NK cells
Karnell *et al.*[8]	2017	Phase II clinical trial	N/A	23	N/A	RRMS	35	F = 16 M = 7	N/A	BEAM regimen	*Regulatory cells* 6mo: maintained at baseline 2yr: maintained at baseline *CD4 cells* *Naive cells* 2-6mo: ↓ 1yr: returned to baseline *Memory cells:* Central memory cells: 6mo: ↓ from baseline 1yr: ↑ but did not return to baseline Effector memory cells: 6mo: ↑ from baseline 2yr: ↓, but maintained above baseline *Effector cells:* 2-6mo: ↑ 2yr: returned to baseline *CD8 cells* Naive cells: 2-6mo: ↓ 2yr: returned to baseline *Memory cells* Effector memory cells: 2-6mo: ↑ from baseline 1yr: began to ↓, but did not return to baseline Central memory cells: 2-6mo: ↓ 1yr: began to ↑, but did not return to baseline *Effector cells* 2-6mo: ↑ 2yr: returned to baseline	*Total B cells* 2-6mo: ↓ 1yr: ↑ from baseline 2yr: ↑ from baseline *Naive cells* 2-6mo: ↓ 1yr: ↑ from baseline 2yr: ↑ from baseline. *Plasma cells* 2-6mo: ↓ 1yr: ↓ and did not return to baseline 2yr: ↓ and did not return to baseline *Memory cells* 2-6mo: ↓ 1yr: ↓ and did not return to baseline 2yr: ↓ and did not return to baseline	*NK cells* 2-6mo: began to ↑ 1yr: returned to baseline
Fassas *et al.*[9]	1999	Clinical trial	N/A	24	N/A	SPMS (primary & secondary), PRMS	40	F = 12 M = 12	10.5	BEAM regimen	*CD4 cells* 1-2yr: ↓ from baseline	N/A	N/A
Moore *et al.*[10]	2018	Prospective phase II clinical trial	Single center	35	N/A	RRMS, SPMS	37	F = 24 M = 11	8.5	BEAM regimen	*Regulatory cells* 2-6mo: ↑ from baseline 1yr: ↑ from baseline *CD4 cells* 2-6mo: ↓ from baseline 1yr: ↑ but did not return to baseline *CD8 cells* 2-6mo: ↑ from baseline 1yr: ↑ from baseline	N/A	2-6mo: ↑ from baseline 1yr: ↑ from baseline
Nash *et al.*[11]	2017	Prospective Phase II clinical trial	multi-center	25	N/A	RRMS	37.3	F = 17 M = 8	5.7	BEAM regimen	*CD4 cells* 3yr: returned to baseline *CD8 cells* Memory cells: 2-6mo: returned to baseline *Naive cells* 1yr: returned to baseline	2-6mo: returned to baseline	N/A

Nash *et al.*[12]	1998	Phase II clinical trial	Fred Hutchinson Cancer Research Center	26	N/A	PPMS, SPMS, RRMS	42.38	F = 12 M = 14	8.55	BEAM regimen	*CD4 cells* 2-6mo: ↑ from baseline 1yr: ↑ from baseline 2yr: ↑ from baseline *CD8 cells* 2-6mo: ↑ from baseline 1yr: maintained above baseline 2yr: maintained above baseline	*Total B cells* 2-6mo: ↑ from baseline 1yr: ↑ from baseline 2yr: ↓ but maintained above baseline	2-6mo: ↑ at 2mo, began to ↓ at 3mo but maintained above baseline at 6mo 1yr: ↑ and maintained above baseline 2yr: ↓ but maintained above baseline
Burman *et al.*[13]	2013	Case–control study	Uppsala University Hospital	12	9	RRMS	32	F = 8 M = 4	7.83	BEAM regimen	*Regulatory cells* ↓ from baseline *CD4 cells* ↓ from baseline *CD4 memory cells* ↑ from baseline	N/A	N/A
Muraro *et al.*[14]	2005	Clinical trial	N/A	7	N/A	PRMS, RRMS, SPMS	43.86	F = 2 M = 5	N/A	myeloablative	*CD4 cells* Naive cells: 2-6mo: ↓ from baseline 1yr: ↑ and returned to baseline 2yr: ↑ from baseline. Memory cells: Central memory cells: 2-6mo: ↓ from baseline 1yr: ↑ but did not reach baseline 2yr: ↓ and did not reach baseline Effector memory cells: 2-6mo: ↑ from baseline 1yr: ↓ but maintained above baseline 2yr: ↓ from baseline. *CD8 cells:* Naive cells: 2-6mo: ↓ from baseline 1yr: ↓ and is below baseline 2yr: ↑ from baseline Memory cells: Central memory cells 2-6mo: ↑ from baseline 1yr: ↓ from baseline 2yr ↓ from baseline Effector memory cells 2-6mo: ↑ from baseline 1yr: ↓ from baseline 2yr ↑ and returned to baseline	Maintained at baseline	Maintained at baseline
Abrahamsson *et al.*[16]	2013	Clinical trial	Chicago, USA	12	7	MS	35	F = 3 M = 9	5.79	non-myeloablative	*Regulatory cells* 2-6mo: ↑ from baseline 1yr: ↓ but maintained above baseline 2yr: ↑ from baseline *CD4 cells* Naive cells: 2-6mo ↓ from baseline 1yr: ↑ from baseline 2yr ↓ from baseline Memory cells: Effector memory cells 2-6mo: ↑ from baseline 1yr: maintained and is above baseline 2yr: maintained and is above baseline *CD8 cells* Naive cells: 2-6mo: ↓ from baseline 1yr: ↑ but did not reach baseline 2yr: ↓ and did not reach baseline Memory cells:	N/A	2-6mo: ↑ from baseline 1yr: ↓ but maintained above baseline 2yr: maintained above baseline

Table 2

(*Continued*)

First author	Year of study	Study design	Place of study	Intervention (N)	Comparator (N)	Disease type	Mean age (years)	Gender	Mean disease duration years	Conditioning regimen	T cells	B cells	NK cells
											Central memory cells: 2-6mo: ↑ from baseline 1yr: ↓ but is maintained above the baseline 2yr: ↓ and returned to baseline Effector memory cells 2-6mo: ↑ from baseline 1yr: maintained and is above baseline 2yr: ↑ from baseline.		
Viswewaran *et al.*[17]	2010	Phase II clinical trial	N/A	22	18	RRMS, SPMS	35.45	F = 12 M = 10	7.6	BEAM regimen	*CD4 cells* 2-6mo: ↓ from baseline 2yr: returned to baseline *CD8 cells* 2yr: ↑ but did not return to baseline	*Total B cells:* 2yr: ↑but did not return to baseline *Plasma cells* 2yr: ↑ but did not return to baseline *Memory cells* 2yr: ↓ and did not return to baseline	N/A
von Niederhäuse rn *et al.*[18]	2022	Cohort study	N/A	20	25	RRMS, PPMS	N/A	F = 10 M = 10	N/A	BEAM regimen	*Total T cells* 2-6mo: ↓ from baseline 1yr: ↑ and returned to baseline	*Total B cells* 2-6mo: ↑ from baseline 1yr: ↑ from baseline *Naive cells* 2-6mo: ↑ from baseline 1yr: ↑ from baseline *Plasma cells* 2-6mo: ↑ from baseline 1yr: ↓ but is maintained above baseline *Memory cells* 2-6mo: ↑ from baseline 1yr: ↑ from baseline	2-6mo: ↑ at 1mo, ↓ but maintained above baseline at 6mo 1yr: ↓ and returned to baseline
Cull *et al.*[19]	2017	Cohort study	Australia	13	N/A	PPMS, SPMS	45.61	F = 11 M = 2	12.46	Cyclophosphamide, ATG	*Regulatory cells* 2-6mo: ↓ at 3mo, ↑ at 6mo, but is below baseline 1yr: ↑ and returned to baseline *CD4 cells* 2-6mo: ↓ from baseline 1yr: ↑ but did not return to baseline 2yr: ↑ but did not return to baseline *Naive cells* 2-6mo: ↓ from baseline 1yr: ↑ and returned to baseline *CD8 cells* 2-6mo: ↑ and returned to baseline	2-6mo: ↓ at 1mo, ↑ and returned to baseline at 6mo	N/A
Arruda *et al.*[20]	2016	Cohort study	Brazil	37	N/A	RRMS, PPMS, SPMS	39.195	F = 26 M = 11	N/A	Cyclophosphamide, ATG	*Regulatory cells* 2-6mo: ↑ from baseline 1yr: ↑ from baseline 2yr: ↑ from baseline *CD4 cells* 2-6mo: ↓ from baseline 1yr: ↑ but did not reach baseline 2yr: ↑ but did not reach baseline Naive cells: 2-6mo: ↓ from baseline 1yr: ↑ but did not reach baseline 2yr: ↑ but did not reach baseline Memory cells: Central memory cells: 2-6mo: ↓ from baseline	*Total B cells* 2-6mo: ↑ from baseline 1yr: ↑ from baseline 2yr: ↓ but maintained above baseline	N/A

												1yr: ↑ but did not reach baseline 2yr: ↑ but did not reach baseline Effector memory cells: 2-6mo: ↑ at 3mo, ↓ from baseline at 6mo 1yr: ↓ from baseline 2yr: returned to baseline *CD8 cells* 2-6mo1yr: ↑ at 3mo, ↓ at 6mo but maintained above baseline 1yr: maintained above baseline 2yr: maintained above baseline Naive cells: 2-6mo: ↓ from baseline 1yr: ↓ from baseline 2yr: ↑ but did not return to baseline Memory cells: Central memory cells: 2-6mo: ↑ at 2mo, ↓ but maintained above baseline at 6mo 1yr: ↓ but maintained above baseline 2yr: maintained above baseline Effector memory cells: 2-6mo: ↑ from baseline 1yr: maintained above baseline 2yr: ↓ but maintained above baseline			
Darlington *et al.*[21]	2018	Cohort study	N/A	24	N/A	RRMS, SPMS	34	F = 14 M = 10		High-dose busulfan, cyclophosphamide, and ATG	*CD4 cells* 2-6mo: ↓ from baseline 1yr: ↑ but did not return to baseline 2yr: ↑ but did not return to baseline	N/A	2-6mo: ↓ from baseline 1yr: ↑ and returned to baseline 2yr: ↑ from baseline
Fassas *et al.*[22]	2014	Phase I/II clinical trial	N/A	85	N/A	PPMS, SPMS, RRMS	39	F = 52, M = 33	7	BEAM regimen	*CD4 cells* 2-6mo: ↓ from baseline 1yr: ↑ but did not return to baseline 2yr: ↑ but did not return to baseline	N/A	N/A
Darlington *et al.*[23]	2013	Cohort study	Canada	14	N/A	SPMS	32	F = 9, M = 5	6.1	Cyclophosphamide, G-CSF, ATG	*Regulatory cells* 2-6mo: maintained at baseline 1yr: ↑ above baseline 2yr: ↑ above baseline *CD4 cells* 2-6mo: ↓ from baseline 1yr: ↑ but did not return to baseline 2yr: ↑ but did not return to baseline Naive cells: 2-6mo: ↓ from baseline 1yr: ↑ but did not return to baseline 2yr: ↑ but did not return to baseline *Memory cells* Central memory cells: 2-6mo: ↑ but did not reach baseline 1yr: ↑ but did not reach baseline 2yr: ↓ and did not return to baseline Effector memory cells: 2-6mo: ↑ but did not reach baseline 1yr: ↑ but did not reach baseline 2yr: ↑ from baseline *CD8 cells* 2-6mo: ↓ from baseline 2yr: ↑ and returned to baseline Naive cells:	2-6mo: ↓ from baseline 1yr: ↑ and returned to baseline	2-6mo: ↓ at 3mo, ↑ at 6mo but did not reach baseline 1yr: ↑ and returned to baseline

Table 2

(*Continued*)

First author	Year of study	Study design	Place of study	Intervention (N)	Comparator (N)	Disease type	Mean age (years)	Gender	Mean disease duration years	Conditioning regimen	T cells	B cells	NK cells
Ruder *et al.*[24]	2021	Cohort study	Switzerland	2	n/a	RRMS	27	52% males 48% female	15	Myeloablation	2-6mon: ↓ from baseline 1yr: ↓ from baseline 2yr: ↓ and did not return to baseline *Memory cells:* Central memory cells: 2-6mo: ↑ from baseline 2yr: maintained above the baseline Effector memory cells 2-6mo: ↑ from baseline 2yr: maintained above the baseline *CD4 cells* 2-6mo: ↓ at 1mo, but returned to baseline by 6mo 1yr: ↑ from baseline 2yr: ↑ from baseline *CD8 cells* 2-6mo: ↓ from baseline 1yr: ↑ and returned to baseline	N/A	2-6mo: ↑ and returned to baseline 2yr: ↑ from baseline
Muraro *et al.*[25]	2014	Phase II clinical trial	USA	2	N/A	N/A	N/A	N/A	N/A	Myeloablation	*CD4 cells* Naive cells: 2-6mo: ↓ from baseline 2yr: ↑ but did not return to baseline Memory cells: 2-6mo: ↓ from baseline 2yr: ↑ but did not return to baseline *CD8 cells* Naive cells: 2-6mo: ↑ 2yr: ↑ and returned to baseline Memory cells: 2-6mo: ↑ at 2mo and returned to baseline at 6mo	N/A	N/A

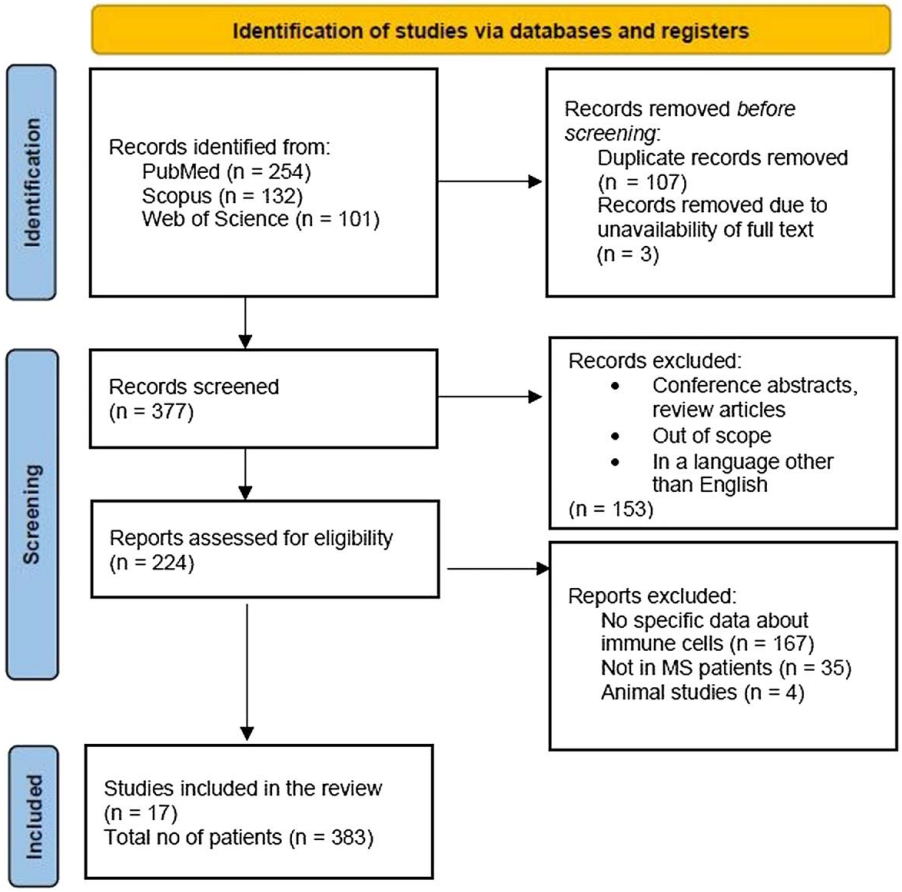

Figure 1. PRISMA flowchart depicting the screened articles. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Although the exact immune mechanism that causes MS is still unknown, current research indicates that proinflammatory T cells, such as CD4 + TH cells that secrete IFN, and IL-17 alone are involved in the process. It is also believed that CD8 + T cytotoxic cells, B cells, and macrophages contribute to the immunological mechanism in MS. In light of this, the application of AHSCT to MS aims to destroy the atypical adaptive immune system through the conditioning regimen and then rebuild the immune system in anticipation of the restoration of immunological tolerance[32]. In patients with aggressive types of MS, immunoablation followed by rescue with AHSCT has been found to completely stop all detectable CNS inflammatory activity[33]. The most typical method for ablating the immune system and, to varying degrees, the myeloid system is high-dose conditioning using a combination of cytotoxic medicines. The autologous hematopoietic graft is then reinfused (transplanted). ATG is frequently given along with the conditioning regimen to deplete T cells; due to the long half-life of ATG, it will also deplete and prevent the engraftment of any T cells present in the autologous graft[32].

Table 3

Table depicting the proportion of articles that reported the return to or increase above baseline for each immune cell to baseline in 2–6 months, 1 year, and 2 years

Immune cells	2–6 months	1 year	2 years
T regulatory cells	71.4%	100%	100%
Total CD4 cells	20%	–	33.3%
CD4 naive cells	–	57.1%	–
CD4 effector memory cells	60%	–	80%
CD4 central memory cells	100%	100%	100%
Total CD8 cells	66.7%	100%	100%
CD8 naive cells	14.3%	42.9%	50%
CD8 effector memory cells	100%	–	100%
CD8 central memory cells	66.7%	66.7%	60%
Total B cells	71.42%	100%	–
NK cells	62.5%	100%	100%

In several clinical trials and observational studies, AHSCT has demonstrated positive outcomes, including reduced disease activity, improved neurological function, and lower EDSS scores. According to Chen *et al.*[34], the median EDSS scores measured at every follow-up year post-AHSCT were lesser than the baseline EDSS. In a study with longer follow-up, 17% did not have EDSS changes, and 27% had improvement from baseline[35]. The remaining 56% started with an improved EDSS after transplant and then had a slowly progressive EDSS[34]. According to Saccardi *et al.*[36], the EDSS at follow-up improved in 63% of cases, but in 37% of patients it worsened. The efficacy of AHSCT based on EDSS scores depends on factors like age as well as the

type of MS. Younger age and relapsing forms of MS are associated with more improvement in EDSS scores[37].

The effect of AHSCT is more evident in the T cell population compared to B cells, as examined in this current review. Compared to the B cell and CD8 cell counts, the CD4 cell count declines, with a delayed return to the baseline. Trends in cell counts of various immune components at the end of the 6-month, 1-year, and 2-year follow-up period are depicted in Figure 2. The immune reconstitution also depends on the conditioning regimen used before AHSCT. Non-myeloablative conditioning regimens and ATG-based therapies have better immunological outcomes. The lymphoablative regimens also reprogram the immune system, making it difficult for the immune system to mount autoimmune attacks as in MS. The review also points out that the reconstitution of different cell populations does not develop simultaneously. As observed in the study, T regulatory cells are reconstituted early compared to other T cell populations, responsible for the remission of the disease. While CD4 cells are replenished by the end of a 2-year follow-up period. According to a study by Gosselin and Rivest[28], the reconstitution of T cells occurs in two phases. Phase I lasts for 3 months and is characterized by an increase in T regulatory and effector memory cell population and a decrease in CD4 cell population. Phase II is characterized by reconstitution of CD4 and CD8 cells to pretreatment levels. As observed in the current review, there is a decline in CD4 naive cell count and central memory cells, and an increase in effector memory within 6 months following AHSCT. According to a study, residual naive cells are transformed into effector memory cells, leading to a decline in naive cell count and an increase in effector memory cell count[38]. CD27 + cells from AHSCT recipients also have an increased propensity to get converted into effector memory cells, compared to central memory cells, leading to a decrease in central memory cell count. However, this increases the susceptibility of individuals to infectious episodes, leading to further conversion of central memory cells into effector memory cells[39].

According to a study, a subset of B cells is also involved in the pathogenesis of the disease. AHSCT also targets the B cell population; however, they are replenished by 6 months following AHSCT. This replenishment is due to the proliferation of immature cells rather than memory cells.

Ablation followed by effective reconstitution of immune cells leads to remission of MS. While, faulty reconstitution leads to many complications, including anaphylactic reactions, autoimmune conditions, neutropenic fever, infections and sepsis, gastrointestinal toxicity, and viral reactivations[37].

Thyroid-related complications from AHSCT can lead to autoimmune thyroiditis, which can be either hypothyroidism or

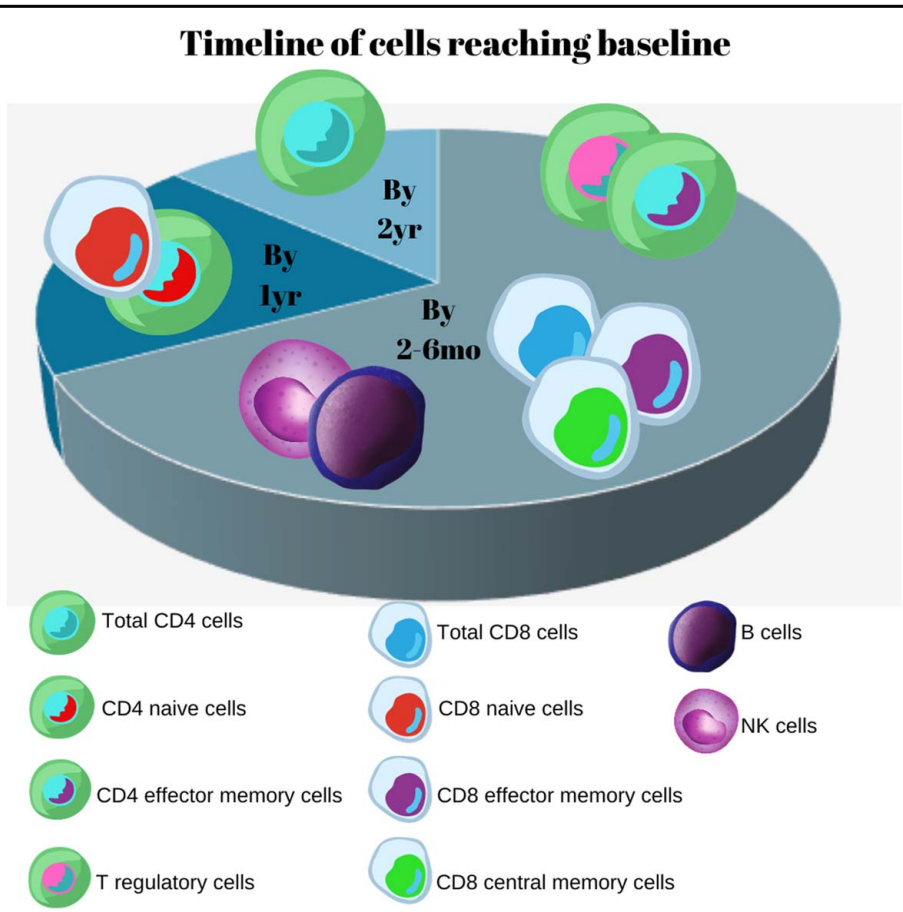

Figure 2. Image depicting the time taken by different immune cells to reach baseline after AHSCT. B cells, NK cells, CD8 central memory cells, CD8 effector memory cells, total CD8 cells, CD4 effector memory cells, and T regulatory cells returned to baseline by 2–6 months. CD8 naive cells and CD4 naive cells returned to baseline by 1 year. Total CD4 cells returned to baseline by 2 years. AHSCT, autologous hematopoietic stem cell transplantation.

hyperthyroidism. Regular monitoring of thyroid function and hormone levels is important, and if necessary, hormone replacement therapy or other appropriate treatments can be administered. Platelet-related complications include autoimmune thrombocytopenia, also known as immune thrombocytopenic purpura (ITP), which is a potential autoimmune consequence of AHSCT. Treatment options for ITP include corticosteroids, immunoglobulin therapy, or other immunosuppressive agents to help normalize platelet levels. Erythrocyte-related complications include autoimmune hemolytic anemia (AIHA), where the immune system mistakenly attacks and destroys red blood cells. AHSCT can trigger AIHA, leading to anemia. Treatment may involve corticosteroids, immunosuppressive drugs, or, in severe cases, blood transfusions. The occurrence and severity of these autoimmune diseases can vary from person to person[40].

AHSCT also predisposes individuals to infections. Viral infection, in particular reactivation of certain herpes viruses (including Varicella–Zoster virus), human herpes virus, cytomegalovirus, and Epstein–Barr virus, is not uncommon. In some instances, antiviral medication is given prophylactically to prevent certain reactivations in high-risk individuals. Fever and infections can easily aggravate symptoms and trigger pseudorelapses. These usually are transient fluctuating symptomatology that patients may have experienced in the past from previous MS attacks and can happen at any time during the transplant process. The treatment of these symptoms is supportive and should focus on patient reassurance, hydration, analgesia, sleeping aids, and spiritual or psychological support[41].

Limitations

The scarcity of research on AHSCT in MS patients undermines our studies' inference and the representativeness of our findings. Several original research articles were excluded due to incomplete data. Very few studies have reported the complete immunological picture. Our study provides a current, exploratory overview of the data even though the data from more extensive, well-designed studies are not yet accessible.

Conclusion

Autologous hematopoietic stem cell therapy is a therapeutic option that can induce rapid and sustained remission of MS. It is one of the highly effective and relatively safe treatments for DMT-resistant MS. After AHSCT, delayed and dysfunctional immune reconstitution has been linked to considerable morbidity and death, including infections and recurrence. The most common adverse events were febrile neutropenia, sepsis, and viral reactivations. Long-term adverse events were the development of new autoimmune diseases, mainly thyroid disease. Safety and success rates of AHSCT can be improved by accurate patient selection criteria, the choice of conditioning regimen, and a multidisciplinary team, including supportive care during the peri-transplant and post-transplant periods. Future large-scale clinical trials are necessary to evaluate long-term safety, and efficacy, and to refine the treatment procedures.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author contribution

Y.I., S.S.M.A., and D.A.: study concept or design; N.L.P.A., S.K. A., and P.R.: data collection; S.S.M.A., R.B.S., and S.S.S.P.P.: data analysis; T.G., P.J., and M.S.K.: writing the paper.

Conflicts of interest disclosure

None.

Research registration unique identifying number (UIN)

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Data availability statement

Data sets generated are available upon reasonable request.

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