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Review article

Advances in hematopoietic stem cell transplantation for autoimmune diseases

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ABSTRACT

Autoimmune diseases (ADs) are a collection of immunological disorders in which the immune system responds to self-antigens by producing autoantibodies or self-sensitized cells. Current treatments are unable to cure ADs, and achieving long-term drug-free remission remains a challenging task. Hematopoietic stem cell transplantation (HSCT) stands out from other therapies by specifically targeting ADs that target various cell subpopulations, demonstrating notable therapeutic benefits and resulting in sustained drug-free remission. Since different ADs have distinct mechanisms of action, the comprehensive understanding of how HSCT works in treating ADs is crucial. This review provides a detailed overview of the latest research and clinical applications of HSCT in treating ADs, offering new insights for clinicians aiming to optimize its use for ADs management.

1. Introduction

Autoimmune diseases (ADs), with a prevalence rate of 5%–8% [1], are a group of immune disorders in which the immune system reacts to self-antigens by generating autoantibodies or self-sensitized lymphocytes. This response leads to tissue and organ damage, resulting in systemic and multisystemic diseases. ADs are associated with high rates of mortality and disability rates, significantly impacting patients' quality of life and pose life-threatening risks in severe cases. Current treatments for ADs primarily involve the use of glucocorticoids and immunosuppressants to broadly regulate the immune response. While these treatments can temporarily manage the disease and reduce organ damage, achieving long-term remission and a cure without medication is challenging. Prolonged medication usage can also lead to treatment-resistant ADs. Biological agents, such as cytokine blockers (e.g., anti-TNF-α) and T/B-cell depletion agents, have emerged as additional treatment options for ADs. These agents target specific cytokines and immune cells to

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halt the inflammatory process, thereby improving disease management. Despite advancements in the use of biologic agents for treating ADs, they do not offer a definitive cure, and patients taking these drugs are susceptible to relapses [2,3].

Hematopoietic stem cell transplantation (HSCT) was initially utilized for treating malignant hematological diseases. As stem cell research has advanced, HSCT has also been increasingly employed to treat nonmalignant hematological diseases, ADs, and hereditary diseases. In autologous HSCT (auto-HSCT), there has been a notable increase in its use for ADs [4]. Unlike other treatments, HSCT addresses ADs at their core and simultaneously targets multiple cell subpopulations. For ADs, auto-HSCT is predominantly preferred over allogeneic HSCT (allo-HSCT) because of its lower treatment-related mortality (TRM, which refers to death resulting from complications of medical treatment rather than the underlying disease. In the context of HSCT, TRM often includes deaths caused by infections, organ toxicity, graft-versus-host disease, or other side effects related to the treatment), and a reduced risk of graft-versus-host disease (GVHD) [5]. In 1977, Baldwin et al. reported that HSCT could effectively treat aplastic anemia (AA) caused by rheumatoid arthritis (RA), leading to relief of the clinical symptoms of RA [6]. This finding was groundbreaking, as it demonstrated the potential of autologous bone marrow transplantation (BMT) in curing ADs. In 1997, auto-HSCT was first used to treat patients with uncomplicated systemic lupus erythematosus (SLE) without hematological disorders, resulting in clinical remission [7]. Supported by previous case reports and findings from preclinical studies on mouse models such as experimental autoimmune encephalomyelitis (EAE) and nonobese diabetes (NOD), HSCT has emerged as a specialized therapeutic approach for treating refractory ADs that are resistant to conventional therapy. The utilization of HSCT has been increasing for ADs such as multiple sclerosis (MS), systemic sclerosis (SSc), crohn's disease (CD), systemic lupus erythematosus (SLE), type 1 diabetes (T1D), and other autoimmune disorders, among which HSCT for MS, SSc, and CD has been the subject of extensive research [8–10]. In 1994, the European Group for Blood and Marrow Transplantation Autoimmune Diseases Working Party (EBMT ADWP) collected data on more than 3300 AD patients from 247 centers across 40 countries. Among these patients, 94 % underwent auto-HSCT [4,11]. The significant efficacy of HSCT as a novel treatment approach for refractory ADs has been demonstrated, improving patient prognosis, enabling long-term drug-free remission and making HSCT the only curative therapeutic approach for ADs. Despite its effectiveness, the exact mechanism of HSCT in treating of ADs remains unclear, as different types of ADs have unique mechanisms of action. This article provides a comprehensive review of the mechanisms and clinical applications of HSCT for ADs, offering clinicians insights into optimizing the use of HSCT in AD treatment.

2. HSCT procedures

In brief, HSCT procedures include the following steps: careful patient selection, determination of the graft source, stem cell mobilization and collection by leukapheresis, a conditioning regimen, stem cell infusion, and hematopoietic reconstitution. The most crucial step is conditioning regimens, which can be divided into high-intensity regimens (such as those with total body irradiation (TBI) or high-dose busulfan); intermediate-intensity regimens (such as BEAM or the combination of high-dose CY and antithymocyte globulin (ATG, ATG mainly exerts immunosuppressive effects that regulate the immune system and promote the implantation of hematopoietic stem cells (HSCs) and the development of immune tolerance); and low-intensity regimens (such as CY, melphalan or fludarabine-based regimens) [12]. The toxicity of HSCT is influenced by the severity of the conditioning regimen, necessitating individualized care.

The objective of *in vitro* CD34 selection is to eliminate differentiated, self-reactive lymphocytes. At present, there is no consensus on the choice of CD34, nor is there any prospective comparative study to determine whether CD34 selection should be performed. However, for the purpose of eliminating immune-active cells, multiple prospective randomized studies have employed CD34-selected

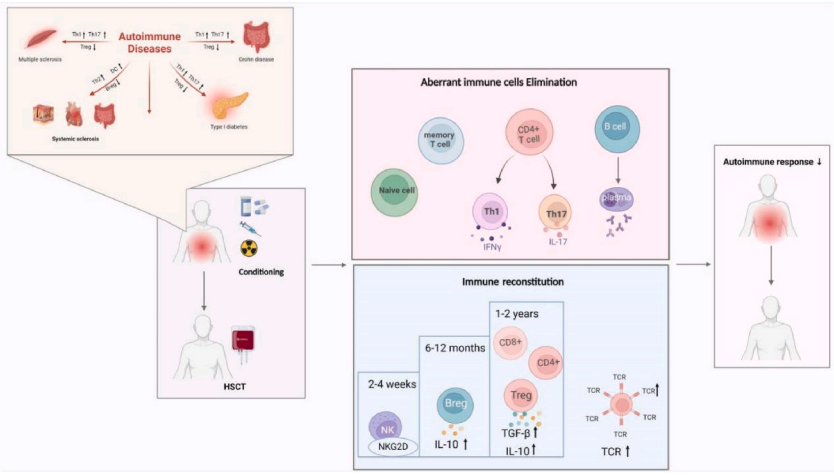

Fig. 1. Mechanism of HSCT in the treatment of ADs.
The pathogenesis of autoimmune diseases and the mechanism of hematopoietic stem cell transplantation in the treatment of autoimmune diseases. Abbreviations: Th1, T helper 1 cell; Th2, T helper 2 cell; Th17, T helper 17 cell; Treg, Regulatory T cell; Breg, Regulatory B cell; DC, Dendritic Cell; NK, Natural Killer; HSCT, hematopoietic stem cell transplantation; TCR, T cell receptor; IL-10, Interleukin-10; TGF-β, Transforming Growth Factor-β.

auto-HSCT and obtained benefits, including Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis (ASTIMS) [13], Autologous Hematopoietic Stem Cell Transplantation for Crohn's Disease (ASTIC) [14], Autologous Stem Cell Transplantation International Scleroderma (ASTIS) [15] and Scleroderma: Cyclophosphamide or Transplantation (SCOT) [16]. Some researchers argue against CD34 selection, citing increased cost and potential infection risk as drawbacks [17,18] Consequently, prospective comparative studies are needed to establish the appropriateness of CD34 selection.

3. How HSCT works

Different ADs exhibit clinical heterogeneity but share common immunological features [19]. ADs are characterized by the activation of polyclonal lymphocytes, the production of autoantibodies, and increased release of inflammatory factors. This immunological profile includes accelerated aging of normal T/B-cell populations, a significant increase in abnormal T/B-cell clones, and thymic degeneration, leading to reduced T-cell receptor repertoire diversity [20,21]. Additionally, plasma cells continue to secrete antibodies that contribute to the progression of ADs [22]. For example, in SSc, B cells overexpress activation markers, persistently produce autoantibodies, and secrete high levels of profibrotic cytokines such as IL-6 and TGF-β1 [23,24].

The cells in the immune system are derived from HSCs, indicating that abnormalities in hematopoietic cells are involved in ADs [25]. The process of auto-HSCT for AD treatment involves three main steps: immune elimination, and hematopoietic and immune reconstitution to restore immune tolerance (Fig. 1). The aim of immune elimination is to eliminate pathological immune cells, creating a conducive environment for the implantation of HSCs. Following HSCT, the process of hematopoietic and immune reconstitution gradually progresses, with different subsets of immune cells recovering at varying rates [26]. The reconstitution process is usually completed within two years. Natural killer (NK) cells recover within 2–4 weeks, B cells recover within 6–12 months, and T-cell subsets take 1–2 years to fully recover [26,27].

3.1. Immune elimination

Pretreatment with immunosuppressants before transplantation also contributes to immune elimination. The primary function of immune elimination is to remove pathological immune cells and minimize the activity of abnormally reactive lymphocytes, including naïve and memory T cells; autoreactive T cells (particularly $CD4^+$ T cells) [26,28,29]; and proinflammatory cytokines such as IL-12, IL-17, IL-2 and IFN-γ [30–32]. Interestingly, among $CD4^+$ T cells, type 1 T helper (Th1) and type 17 T helper (Th17) cells, which characterize the aberrant immune responses in T1D [29], MS [31,32], and CD [33–36], were found to be predominantly cleared. Furthermore, a decrease in the number of IL-6- and TGF-β-producing B cells has been observed [37]. In addition, HSCT can exert a therapeutic effect by reducing the secretion of autoantibodies by plasma cells.

A French cohort study revealed reduced anti-Scl-70 levels in 7 patients following transplantation [38]. Two additional studies yielded comparable results [39,40].

3.2. Immune reconstitution

3.2.1. T cells

T cells recover within 1–2 years after transplantation, with the function of nonthymus-dependent $CD8^+$ T cells being restored prior to the function of thymus-dependent $CD4^+$ T cells. Furthermore, the origins of newly formed $CD4^+$ and $CD8^+$ T cells differ. Memory $CD4^+$ T cells predominantly survive in the early stages of transplantation, but after auto-HSCT, the T-cell repertoire is completely renewed [41]. Additionally, high-throughput deep sequencing of the TCR-β chain, both before and after HSCT, has shown that after the elimination of autoreactive T cells, $CD4^+$ T cells arise from newly formed cells, whereas $CD8^+$ T cells are mainly clonal expansions of preexisting memory cells [42].

3.2.2. Regulatory T cells

Regulatory T (Treg) cells play a critical role in immune reset following HSCT [37,43]. It has been confirmed that Treg cell numbers increase after HSCT [44]. In both the EAE and NOD mouse models [45], HSCs restore Treg cell development, thereby increasing the Treg cell population. After HSCT, patients with immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome and T1D show less insulin dependency, demonstrating that HSCT can increase the Treg cell pool and thus prevent the destruction of β cells [46]. Zhang et al. [47] reported that inhibiting the PI3K/Akt signaling pathway through a combination of HSCT and a phosphatidylinositol 3-kinase (PI3K) inhibitor in T1D mice helps maintain Treg cell homeostasis, facilitating long-term remission in T1D patients post-HSCT. Therefore, the immune reset of Treg cells post-HSCT has a significant effect on alleviating symptoms of ADs.

Studies suggest that the expanded Treg cell population post-HSCT originates from the reactivated thymus [48] or is stimulated by ATG during pretreatment [49]. After auto-HSCT, the expression levels of GITR and CTLA-4 are elevated [43], and auto-HSCT can induce major histocompatibility complex (MHC) mismatch. MHC mismatching promotes mixed chimerism in the thymus, leading to the loss of host-type autoreactive T cells and an increased proportion of Foxp3+ Treg cells [50], as well as an increase in PD-L1 expression on host-type plasmacytoid dendritic cells (pDCs) [50–52]. This process establishes a tolerance network between Treg cells and dendritic cells (DCs) [53], in which autoreactive T cells are actively tolerated and immune tolerance is induced in peripherally unresponsive autoreactive T cells [50]. These findings indicate that auto-HSCT can induce high expression of GITR and CTLA-4 while establishing a tolerance network, facilitating the functional recovery of Treg cells.

Moreover, other studies have shown that, post-HSCT, patients who respond have greater numbers of Treg cells and regulatory B

(Breg) cells, as well as greater levels of IL-10 in their peripheral blood than before transplantation [43,54]. This indicates that Treg/Breg cells, by producing the anti-inflammatory cytokines IL-10 and TGF-β, prevent the activation of T cells that have escaped other tolerance mechanisms. Additionally, Treg cells can suppress the Th1 or Th17 cells that mediate various immune diseases [55], thereby restoring the balance of T-cell subgroups and thus treating ADs. Treg cells are critical factors for achieving long-term remission post-HSCT. Notably, in the treatment of CD patients, Treg cells post-HSCT also reduce abnormal immune responses against the commensal microbiota or dietary antigens [33], significantly decreasing the number of M1 macrophages and neutrophils in the mucosa [26] and playing a vital role in maintaining intestinal mucosal homeostasis.

3.2.3. TCR repertoire

Following HSCT, HSCs reactivate the thymus to promote the generation of lymphoid progenitors and reconstruct the T-cell repertoire, increasing the diversity of T-cell receptors [48,56]. Sequencing has revealed that the dominant TCR clones of $CD4^+$ T cells, previously detectable in the peripheral blood before treatment, are no longer detectable after immunological reconstitution post-HSCT [42]. Additional findings [57] suggest that replacing the preexisting TCR repertoire is a mechanism of the effect of auto-HSCT in treating relapsing/remitting MS (RRMS). Based on these findings, the use of peripheral blood as a surrogate for cerebrospinal fluid in future research on mechanisms associated with auto-HSCT efficacy has been proposed. A follow-up study of 31 patients with SSc post-transplantation indicated that, compared with nonresponsive patients, responsive patients had less overlap in the TCR repertoire before and after transplantation [43]. Moreover, compared with pre-HSCT, the TCR repertoire is expanded by 500–20,000 unique TCR sequences post-HSCT [43]. These results collectively demonstrate that HSCT resets and increases the clonality of the TCR repertoire and that the clonality of the TCR repertoire can be utilized to assess the efficacy of auto-HSCT. The renewal of the TCR repertoire after auto-HSCT has been proposed as a potential biomarker of treatment response, where patients with favorable clinical outcomes after auto-HSCT exhibit lower TCR clonal overlap [42].

3.2.4. B-cell subsets and cytokines

Unlike T cells, B cells recover within 6–12 months post-transplantation, with an increased proportion of CD27-IgD^+ naïve B cells [43], consistent with transcriptomic results [17] and potentially related to the expansion of the naïve B-cell compartment [43]. Early after HSCT, regenerated B cells may originate from residual bone marrow-derived cells or HSCs, but in later stages, they are derived primarily from HSCs [48,58]. Changes also occur in Breg cells following auto-HSCT. After auto-HSCT, the number of Breg cells increases, and these cells produce higher levels of IL-10 than before transplantation [43]. Research has shown that IL-10 production by Breg cells requires the activation and phosphorylation of the proteins ERK1/2, p38-MAPK, and STAT3 [59]. Júnior et al. [37] studied the phosphorylation of these signaling molecules in B cells and reported increased phosphorylation of ERK1/2 and p38-MAPK after auto-HSCT but no improvement in the phosphorylation of the STAT3 protein, suggesting that auto-HSCT may enhance Breg function through increased phosphorylation of ERK1/2 and p38 MAPK. Furthermore, auto-HSCT primarily restored the suppressive ability of $CD19^+CD24^{high}CD38^{high}$ Breg cells, inhibiting the production of Th1 cytokines by $CD4^+$ T cells.

3.2.5. NK cells

Thymus-dependent T-cell regeneration and immune regulation mediated by T cells and natural killer (NK) cells are the primary pathways currently known to influence immune reconstitution following autologous immune disease transplantation. NK cells are the quickest and earliest to recover after HSCT, beginning to recover within 2–4 weeks. NK cells rapidly regenerate and increase in number post-HSCT [27,32,60], whereas Th17 cells significantly decrease following auto-HSCT. Removing NK cells from mononuclear cells in peripheral blood *in vitro* after auto-HSCT leads to an increased Th17 cell response, indicating that NK cells can regulate Th17 activity [32,61]. Moreover, NK cells reduce the proportion of Th17 cells via an NKG2D-dependent mechanism [32]. Consequently, the rapid reconstitution of NK cells after auto-HSCT helps suppress the re-emergence of Th17 cells, benefiting long-term remission and a potential cure in MS patients [32,62].

3.2.6. Apoptosis

Abnormal apoptosis is linked to the pathogenesis of various ADs [63]. In the central nervous system (CNS), increased T-cell survival could be facilitated through mechanisms such as the Fas/FasL system and increased myelin destruction. Oliveira et al. [64] reported that auto-HSCT leads to the upregulation of Fas/FasL and the downregulation of the expression of the antiapoptotic gene BCL-xL in peripheral blood mononuclear cells (PBMCs). An analysis of apoptosis-related molecules in MS patients before and after auto-HSCT and a two-year follow-up [65] revealed that auto-HSCT plays a crucial role in the early stages of apoptotic mechanism reconstitution and that normalization of apoptosis-related molecules is associated with early treatment outcomes. This may contribute to the reconstruction of immune tolerance in the first two years after treatment. Thus, Fas and FasL could be identified as biomarkers for clinical neurological prognosis in MS patients who undergo auto-HSCT and could become targets for future therapeutic interventions [64].

4. Research progress in HSCT for ADs

4.1. In vivo animal models

Since the late 1980s, HSCT has been identified as a potential treatment for ADs through incidental clinical findings. HSCT has proven effective across various autoimmune experimental models. Common animal models include EAE for studying the acute/

relapsing phases of MS; 2,4,6-trinitrobenzenesulfonic acid-induced colitis for inflammatory bowel disease (IBD) research; NOD mice, which are used for T1D research; and chronic adjuvant-induced arthritis (CIA) for investigating rheumatoid arthritis (RA). These models are utilized to explore the underlying mechanisms of ADs and to investigate the efficacy and mechanisms of action of various treatment methods, serving as preclinical "probes."

The concept of treating ADs with auto-HSCT originated in 1985 when mice with ADs underwent lethal radiation treatment followed by syngeneic and allogeneic BMT, leading to marrow reconstruction [25]. Moreover, newly formed T cells exhibit tolerance toward cells expressing both donor and host MHC determinants [66]. In 1989, Dirk and colleagues [67] reported that high-dose total body irradiation (TBI) followed by BMT in an adjuvant-induced arthritis model resulted in the complete disappearance of synovial inflammation histologically and induced long-term remission, with both syngeneic and allogeneic bone marrow transplants being equally effective. In 1992, Karussis et al. used myeloablative cyclophosphamide (CY) or TBI followed by autologous BMT and reported that HSCT could suppress the progression of EAE [68] and even reverse established chronic relapsing EAE (CR-EAE), suppressing or improving the symptoms of paralysis relapses [69–71] while inducing long-term antigen-specific tolerance and achieving long-term remission [72]. A 2010 study in Brazil on experimental animal IBD showed that both HSCT and CY could significantly reduce the histopathological features of colitis, and high-dose CY followed by HSCT could regulate mucosal immunity and accelerate immune reconstitution [36].

In summary, preclinical studies have demonstrated that HSCT is effective in treating ADs and can induce long-term tolerance. However, these studies reported that using lethal TBI or CY as a conditioning regimen carries significant risks. Therefore, it is necessary to develop less toxic conditioning regimens, such as nonmyeloablative HSCT. In foundational research on T1D, nonmyeloablative conditioning regimens are often used. After such conditioning, allo-HSCT establishes a mixed chimeric state of MHC mismatch in NOD mice, reversing their autoimmune response [50,73,74] and inducing tolerance to donor islets in NOD mice, enabling them to accept donor islet transplants and completely cure diabetes [74]. Moreover, our team [53] induced mixed chimerism in T1D mice through haploidentical HSCT, successfully correcting the autoimmune activation state and thereby curing T1D, with clinical manifestations and histopathological features returning to normal in all experimental mice (>100 instances) without any symptoms of GVHD. In terms of mechanism exploration, this was the first study to reveal the complex interactions between donor and recipient T cells, Treg cells, and DCs within a chimeric mixture, providing new insights for other autoimmune and immune tolerance-related research with promising clinical translational prospects. Additionally, haploidentical mixed chimerism combined with gastrin and epidermal growth factor (EGF) can stimulate the reactivation and regeneration of insulin β cells, curing T1D [75,76]. Inducing MHC-mismatched mixed chimerism can also be used to treat other ADs, such as SLE [77] and MS [78].

Furthermore, Kornioti et al. [79] focused on functional subsets of HSCs and proposed a new hypothesis that HSC subsets could play an active immunoregulatory role in treating ADs. By utilizing G-CSF and Flt3 ligand (Flt3-L), HSCs are synergistically mobilized from the bone marrow to the periphery, enriching multipotent progenitor cells (MPPs). It has been demonstrated that MPPs primarily exert their unique regulatory effects by expanding $Foxp3^+$ Treg cells, thus preventing EAE. In the future, MPPs could serve as a supplementary therapeutic approach to auto-HSCT.

4.2. *Multiple sclerosis*

MS is a chronic demyelinating disease of the CNS characterized by autoimmune, inflammatory, and neurodegenerative effects. It involves myelin-specific autoreactive lymphocytes attacking the myelin sheath and axonal structures. Since 1995, HSCT has been employed in the clinical treatment of MS. To date, from the first phase II randomized controlled trial, ASTIMS [13], reported that in 21 patients with RRMS and secondary progressive MS (SPMS), those treated with auto-HSCT showed a 79 % reduction ($P < 0.001$) in relapses and new T2 lesion counts on MRI compared with those receiving mitoxantrone, indicating the superior efficacy of auto-HSCT. The first large RCT phase III study for RRMS, MIST, has significantly increased the evidence base. In this preliminary study, nonmyeloablative HSCT ($n = 55$) was more effective than disease-modifying therapy (DMT) ($n = 55$) for patients with RRMS [80]. Other studies on auto-HSCT for MS patients are observational cohort studies that assess efficacy by comparing disease activity before and after transplantation [81–83]. The Expanded Disability Status Scale (EDSS) and post-treatment MRI scans were used to measure disease severity.

Currently, conditioning regimens for auto-HSCT vary in intensity: high, intermediate, and low. High-intensity immunosuppressive regimens, which are myeloablative and typically include high-dose TBI combined with CY and both *in vivo* and ex vivo T-cell depletion, were more commonly used in early trials [83–87]. However, myeloablative regimens are often accompanied by infections and significant treatment-related mortality [88]. Due to these concerns, intermediate-intensity conditioning regimens such as BEAM (BCNU, cytarabine, melphalan, and etoposide), which exhibit better tolerability and lower morbidity and mortality rates, have been introduced [13,80,89]. Conversely, some study studies do not support the use of the BEAM + ATG conditioning regimen. A long-term retrospective study revealed [90] that in RRMS patients, the use of the BEAM + ATG regimen was independently associated with a reduced risk of no evidence of disease activity-3 (NEDA-3) failure [HR = 0.27 (0.14–0.50), $p < 0.001$], indicating that the BEAM + ATG regimen is associated with more significant suppression of clinical relapses and MRI inflammatory activity. Another study [91] comparing the BEAM + ATG regimen with the CY/rATG regimen revealed that the CY/rATG regimen appears to be less toxic and effective. Thus, nonmyeloablative regimens, such as low-intensity CY and ATG, have been introduced. These nonmyeloablative approaches selectively target lymphoablation without irreversibly impairing the regenerative capacity of the bone marrow. A nonmyeloablative CY and antilymphocyte antibody regimen has been safely used by Burt and colleagues [80,92,93] for HSCT in MS patients and for the treatment of many ADs, including SLE, T1D, and SSc. Different regimens produce varying degrees of lymphoablation and marrow clearance, and the treatment response varies among different patient groups. Therefore, it is not feasible to reliably

compare the risk–benefit ratios among the three regimens to establish a unified approach. Different auto-HSCT conditioning regimens can be selected based on patient conditions and needs, allowing for personalized treatment.

Furthermore, auto-HSCT may be most beneficial for patients with RRMS or those with milder symptoms [80,92,94]. Burt and colleagues [92] reported excellent efficacy in RRMS patients, with 81 % showing decreases in EDSS scores after treatment. In a large single-center retrospective study [85] ($n = 145$), one-third of the patients (primarily those with RRMS and mild to moderate disability) showed improvement in disability scores two years after auto-HSCT. Conversely, for other subtypes or patients with higher pretransplantation disability scores, auto-HSCT was ineffective [88,93]. A phase I/II trial [88] involving 21 patients with rapidly progressive MS revealed that TBI combined with HSCT was ineffective for patients with progressive disease and high pretransplantation EDSS scores (>6.0). However, in a retrospective analysis [95] of SPMS patients treated with HSCT vs. 1975 treated with other DMTs [79], 61.7 % of auto-HSCT patients had no disability progression within five years [i.e., no chronic progressive disease (CPD)], and their EDSS scores tended to be lower over 10 years than those of patients treated with other DMTs ($p < 0.001$). These results suggest that, compared with standard immune therapies, auto-HSCT can slow disability progression in younger patients with active SPMS and increase the likelihood of disability improvement.

In 2015, Burt et al. [93] studied 145 MS patients. Two years following auto-HSCT, 50 % of patients demonstrated significant disability improvement, with no treatment-related fatalities. The four-year relapse-free survival rate was 80 %, and the progression-free survival (PFS) rate was 87 %. Another study [85] reported similar results, with an overall three-year event-free survival rate of 78.4 % without maintenance treatment. The PFS rate was 90.9 %, and the relapse-free survival rate was 86.3 %. In the largest retrospective study conducted by the EBMT-CIBMTR [94], which included 281 MS patients treated with auto-HSCT between 1995 and 2006 at 25 transplant centers, five-year PFS and overall survival (OS) rates of 49 % and 93 %, respectively, were reported. Factors such as younger age, relapsing MS, fewer prior immune treatments, and lower baseline EDSS scores were associated with better outcomes. Within twelve months after transplantation, 52 % of relapsing patients and 31 % of progressing patients experienced neurological improvement. The latest retrospective study [90] included 210 patients, and in RRMS patients, the five-year PFS rate was 85.5 %, and at ten years, it was 71.3 %. Notably, no deaths have been reported in patients who underwent transplantation since 2007, and no treatment-related deaths after auto-HSCT for MS have been reported [62]. Moreover, two multicenter phase II clinical trials [86,87] demonstrated that auto-HSCT can induce long-term sustained remission in patients with active RRMS without any ongoing disease-modifying drugs. auto-HSCT can significantly reduce disability rates, increase survival rates in MS patients, and is associated with high safety.

In conclusion, compared with standard immune therapies, young patients with active SPMS and RRMS are candidates for auto-HSCT treatment, although RRMS is a more suitable indication for HSCT treatment. Moreover, there is no uniformly recommended conditioning regimen, so personalized selection should be made based on the patient's condition and needs.

4.3. Type 1 diabetes

T1D is an AD characterized by T-cell-mediated destruction of pancreatic β-cells. Protecting β-cells from autoimmune attacks and regenerating or replacing β-cells are the goals of T1D treatment. Currently, the primary treatment for T1D involves insulin replacement therapy, which cannot restore pancreatic function or ensure precise blood glucose control, and patients remain at risk for hypoglycemia. Islet or whole pancreas transplantation is considered a curative therapy for T1D, as it can fully restore the pancreatic endocrine function and significantly improve blood glucose control [96]. However, the long-term survival rate of transplanted islets is low, and chronic immunosuppression-related side effects and donor shortages limit the application of islet transplantation [97]. Since its first application in T1D treatment in 2003 [98,99], HSCT has been several studied as a promising alternative to islet transplantation [28]. Compared with conventional insulin therapy, auto-HSCT leads to more effective blood glucose control and has a reduced incidence of complications, with confirmed safety and tolerability [29,100–102].

Research findings indicate that auto-HSCT can preserve β-cell function and promote long-term beneficial metabolic effects [101,103,104]. In a prospective phase I/II clinical study [98], nonmyeloablative auto-HSCT was performed on newly diagnosed T1D patients. Fourteen out of 15 patients stopped using insulin, and 13 out of 15 had a glycated hemoglobin (HbA1c) level less than 7 %. This study was the first to demonstrate that HSCT could improve β-cell function in T1D patients, leading to long-term insulin independence and normal HbA1c levels, with low treatment-related toxicity. Couri et al. [99] reported on 23 patients treated with nonmyeloablative auto-HSCT who, after an average follow-up of 29.8 months, showed significantly elevated C-peptide levels, with most patients achieving insulin independence and good glycemic control without any fatalities. Elevated C-peptide levels after transplantation clearly indicate the recovery of islet cells. A multicenter study involving 65 patients revealed [105] that 59 % achieved remission six months after auto-HSCT, and that 32 % remained insulin independent at 48 months. This suggests that HSCT can suppress autoimmunity, including that of the pancreas, reverse the immune-mediated destruction of pancreatic β-cells, promote the regeneration of islet β-cells, and restore β-cell function, thereby achieving a cure.

However, auto-HSCT has shown poor outcomes in T1D patients with diabetic ketoacidosis (DKA) [106]. Among 28 T1D patients treated with auto-HSCT, including 11 with DKA, 15 achieved insulin independence, indicating that auto-HSCT is an effective long-term treatment for insulin dependency. However, the complete remission rate in the non-DKA group was three times greater than that in the DKA group, indicating significant differences. This finding suggests that patients diagnosed with DKA may not be suitable candidates for auto-HSCT.

4.4. Crohn's disease

Crohn's Disease is an immune-mediated chronic IBD characterized by gastrointestinal inflammation and immune dysregulation leading to mucosal lesions [107]. Treatment options for CD include the use of anti-inflammatory drugs, immunosuppressants, steroids, biologics, and surgery, either alone or in combination. Recent therapeutic advances include biologics such as anti-tumor necrosis factor (anti-TNF) agents and novel biologic drugs [108]. Despite the variety of treatment options, many CD patients continue to experience poor outcomes and frequent relapses [2,3]. Most patients require repeated surgical interventions and face risks such as ostomy, short bowel syndrome, and a reduced life expectancy. Therefore, auto-HSCT has been proposed as a promising treatment option. According to the European Society for Blood and Marrow Transplantation registry [109], CD is the third most common type of AD treated with HSCT. In 2003, HSCT was first applied as a standalone treatment for severe CD patients with success [110,111].

In 2015, in the open-label, phase III, randomized, multicenter ASTIC trial [14,112], 45 patients with refractory CD were recruited and randomly assigned to undergo HSCT (n = 23) or control treatment (standard therapy followed by HSCT after one year [n = 22]). After one year, 38 % of patients achieved the primary endpoint, and half achieved endoscopic healing, although no significant difference was observed. However, the high incidence of severe adverse events does not support the widespread use of HSCT in patients with refractory CD. Nonetheless, more patients in the HSCT group were able to discontinue immunosuppressive treatment, and clinical and endoscopic indices of disease activity improved. In the largest single-center cohort to date [26], 50 % of patients achieved endoscopic drug-free remission at the one-year follow-up. Garcia et al. [113] also demonstrated that, despite significant toxicity, HSCT could provide substantial and sustained benefits to patients with refractory CD, suggesting that it is a life-saving treatment. Although most patients relapse within five years of HSCT, 80 % regain responsiveness to medications, and achieve clinical remission.

How can efficacy be increased while reducing toxicity and the risk of relapse? The ASTIC study [14] investigators have suggested that in future trials should evaluate whether the use of low-intensity conditioning regimens can maintain the observed benefits while reducing the risks associated with HSCT. In a phase I/II prospective study [113], low-dose CY (2 g/m^2) was used for nonmyeloablative auto-HSCT in 14 patients. After auto-HSCT, 13 patients achieved remission with a clinical disease activity index (CDAI) of less than 150, and only four experienced complications directly related to transplantation, with no fatalities reported, significantly improving patients' quality of life. The findings of this study indicated that auto-HSCT has low toxicity, few adverse reactions, and minimal adverse events with ensured efficacy. Therefore, future studies should consider the lower doses of CY in mobilization protocols.

In summary, the safety and efficacy of HSCT have gradually been validated [114,115]. HSCT can restore immune tolerance, alleviate symptoms of CD, and restore drug sensitivity in CD patients [33]. auto-HSCT holds a significant place in the treatment of severe, refractory CD patients.

4.5. Systemic sclerosis

SSc is a chronic form of AD characterized by autoimmune activation, inflammation, and increased fibroblast activity, leading to fibrosis of the skin and internal organs and diffuse microvascular changes [116–118]. SSc is clinically divided into two subgroups based on skin involvement: limited cutaneous SSc (lcSSc), where skin fibrosis is localized and progresses slowly, and diffuse cutaneous SSc (dcSSc), which involves rapid progression of skin fibrosis affecting the trunk, limbs, and internal organs [119,120]. The mortality rate of SSc, especially dcSSc, is greater than that of any other rheumatic disease [117]. Complications such as interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), and cardiac involvement can be life-threatening. Current treatments include glucocorticoids, immunosuppressants, biologics, and disease-modifying antirheumatic drugs (DMARDs); however, they fail to achieve sustained efficacy. In recent years, significant progress has been made in using auto-HSCT as a promising treatment for severe, refractory SSc. In 2001, an early multicenter open-label phase I/II study [121], assessed 41 SSc patients who underwent auto-HSCT; 69 % showed a 25 % improvement in skin scores after transplantation, but 17 % died. Vonk et al. [122] selected patients with severe dcSSc for myeloablative auto-HSCT. A total of 73 % of patients showed a significant decrease in the modified Rodnan Skin Score (mRSS) after one year, and 94 % showed a decrease after five years. Post-transplantation improvements in skin thickening and stable organ function continued for up to seven years. These findings confirm the feasibility and acceptable toxicity of auto-HSCT. Another phase I trial [123] using a nonmyeloablative conditioning regimen revealed that at a median follow-up of 25.5 months, the OS rate was 90 %, and the PFS rate was 70 %, with improvements in skin elasticity and no treatment-related deaths.

To date, three randomized controlled trials comparing auto-HSCT with CY have been completed. The American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST) [124] was an open-label phase II trial, revealed sustained improvements in mRSS and forced vital capacity (FVC) lasting two years in 11 SSc patients who underwent nonmyeloablative auto-HSCT, showing superior efficacy to the CY control group. The ASTIS [15] trial revealed that nonmyeloablative treatment plans had a greater long-term event-free survival benefit than 12 months of monthly intravenous CY pulses in patients with dcSSc. In contrast to the two previous nonmyeloablative auto-HSCT randomized controlled trials, the SCOT [16] trial used a myeloablative auto-HSCT approach. At 54 months, the event-free survival rate was 79 % in the transplantation group compared to 50 % in the CY group (P = 0.02). By 54 months, 9 % of participants in the transplantation group began using DMARDs to alleviate disease symptoms, while 44 % in the CY group did (P = 0.001). The treatment-related mortality rates in the transplantation group at 54 and 72 months were 3 % and 6 %, respectively, while they were 0 % in the CY group. Despite anticipated increased toxicity, patients receiving myeloablative auto-HSCT showed an advantage in increasing event-free survival and OS periods. Compared with other ADs, the increased toxicity of HSCT for SSc is attributed primarily to SSc-related cardiac dysfunction (especially PAH) and CY-induced cardiac toxicity [9,118]. Therefore, thorough screening and evaluation of patients are necessary, and stringent cardiopulmonary assessments should be conducted before HSCT to minimize associated risks [125].

This study revealed that both myeloablative and nonmyeloablative auto-HSCT have encouraging outcomes, can stabilize lung, heart, and renal functions, significantly reduce skin involvement [126–128], and improve quality of life [16,129,130]. These outcomes have been linked to longer OS and extended disease-free periods. However, long-term benefits might be sustained more effectively by "nonmyeloablative" methods [131].

Additionally, auto-HSCT has been shown to improve vascular morphology and skin microangiopathy. A comprehensive study on vascular markers in skin biopsies before and after transplantation showed [132] that HSCT could induce neovascularization. Similarly, studies [133,134] have used a noninvasive technique for diagnosing SSc, nailfold videocapillaroscopy (NVC), to monitor patient microvasculature. In conclusion, HSCT can promote vascular remodeling and restore some vascular structures.

4.6. Clinical application of allo-HSCT

Allo-HSCT is extensively used to treat patients with malignant and nonmalignant hematological diseases. Compared with auto-HSCT, allo-HSCT is associated with greater toxicity, such as a greater risk of GVHD. However, allo-HSCT has the advantages of completely replacing abnormal stem cells and autoreactive cells, more effectively eradicating autoreactive cells, and regenerating a healthy immune system that is tolerant to both allogeneic and autologous antigens [135]. Allo-HSCT is primarily used to treat autoimmune cytopenia (AIC) [136] and younger patients [4,137], and it has shown optimal results in treating juvenile idiopathic arthritis (JIA) [138]. A retrospective study [138] evaluated 16 patients with refractory JIA who underwent nonmyeloablative allo-HSCT. Among these patients, 14 survived (median follow-up of 29 months), all showing early improvements in arthritis symptoms, resolution of macrophage activation syndrome (MAS), and improved quality of life. Furthermore, at the last follow-up, 11 children achieved complete drug-free remission. Additionally, Greco et al. [137] conducted a retrospective study of 128 young patients with refractory ADs who underwent allo-HSCT, with a nonrelapse mortality (NRM) rate of 12.7 % at 100 days and OS and PFS rates at five years of 70.2 % and 59.4 %, respectively. This finding indicates that allo-HSCT has the potential for long-term disease control in young patients with refractory ADs, with acceptable toxicity and NRM.

Allo-HSCT can address diseases caused by monogenic innate immune deficiencies that auto-HSCT cannot cure, but the efficacy and outcomes of allo-HSCT depend on better patient selection. Additionally, to facilitate wider application of allogeneic transplantation, it is essential to reduce related complications [139], which requires further research. Current clinical studies on the use of HSCT for treating ADs are summarized in Table 1.

5. Discussion

Over the past two decades, HSCT has evolved from an experimental salvage therapy to a standard treatment option and is currently the only therapy capable of achieving long-term drug-free remission and curing ADs. According to the European Society for Blood and Marrow Transplantation (EBMT), the incidence of ADs is increasing, making them the fastest-growing category for auto-HSCT [11, 140]. Compared with ongoing biologic therapies that require continuous medication, HSCT better aligns with the goal of improving quality of life by offering a potential for a cure.

However, HSCT is an intervention with inherent risks. In the treatment of ADs, auto-HSCT is primarily used because it avoids the risks associated with allo-HSCT, such as GVHD. Still, auto-HSCT can cause complications and fatalities at various stages of the transplantation process (mobilization, conditioning, transplantation, and post-transplantation). In some cases, auto-HSCT is not a permanent solution, as there is a significant risk of relapse after transplantation. However, the intensity of disease activity during relapse is often lower than that it was before treatment, and patients who relapse after receiving stem cell therapy respond better to conventional or biologic treatments than they did before HSCT state do. Even in patients with refractory AD, the severity of the condition may be reduced [141], and sensitivity to previously ineffective treatments may be restored. For example, HSCT can restore responsiveness to TNF-α treatments in patients resistant to anti-TNF-α therapies [14,113,142]. Integrating HSCT with modern targeted biologic treatments opens new avenues and provides innovative therapeutic strategies. For example, research is investigating HSCT in conjunction with vedolizumab to treat CD (NCT03219359). Ultimately, the principal challenge is reducing the recurrence of ADs after auto-HSCT. Currently, the key cellular components or targets responsible for ADs and their relapses remain poorly understood. Further investigation is needed to determine whether the cellular composition after auto-HSCT might become abnormal. Understanding the underlying mechanisms of disease remission and relapse to develop personalized auto-HSCT and post-transplantation treatment plans is crucial for addressing the root causes of recurrence.

The optimal components of the graft used in allo-HSCT are still under investigation. Currently, peripheral blood-derived HSCs are used in most studies. However, a clinical trial (NCT03835312) is now recruiting participants for the use of umbilical cord blood-derived HSCs in the treatment of type 1 diabetes, suggesting that these cells may have potential for allo-HSCT and for treating children and adolescents.

Can adjusting the ratio of cells or selecting dominant subgroups reduce the incidence of GVHD while maintaining therapeutic efficacy? Further study is needed to determine the feasibility of this approach. Currently, implementing cell therapy in conjunction with HSCT appears to be more practicable option. In the treatment of ADs, cell therapies such as chimeric antigen receptor (CAR)-T and regulatory T (Treg) cells are emerging as promising possibilities. CAR-T cells have been applied to ADs caused primarily driven by B cells, such as SLE, and have demonstrated significant efficacy [143]. In patients with hematological malignancies, some patients still face high risks and recurrence rates after standalone CAR-T-cell therapy or HSCT. However, combining CAR-T-cell therapy with allo-HSCT has been shown to significantly increase treatment efficacy and reduce patient risk [144–146]. Despite these findings, no studies have yet explored the combination of both therapies for treating ADs. Treg cells play crucial roles in maintaining self-tolerance

Table 1
Clinical trials summary of HSCT treating autoimmune diseases.

Conditions	Interventions	Pts	Phases	Status	Institutions	Trial number
Multiple sclerosis	NM-AHSCT	110	Phase 2	Completed	Northwestern University, Feinberg School of Medicine	NCT00273364
	NM-AHSCT	21	Phase 1/2	Terminated	Northwestern University	NCT00278655
	HDIT-AHSCT	24	Phase 2	Completed	Ottawa Hospital Research Institute	NCT01099930
	HDIT-AHSCT	156	Phase 3	Recruiting	Stanford Multiple Sclerosis Center	NCT04047628
	HDIT-AHSCT	25	Phase 2	Completed	Ohio State University School of Medicine	NCT00288626
	HDIT-AHSCT	26	Phase 1	Completed	City of Hope National Medical Center	NCT00014755
	CY/rATG vs. CY/rATG/ IVIG AHSCT	66	Phase 3	Terminated	Northwestern University	NCT03342638
	AHSCT	175	Observational Study	Completed	Sahlgrenska University Hospital	NCT05029206
	NM-AHSCT	617	N/A	Invitation	Centro de Hematología y Medicina Interna	NCT02674217
	AHSCT	24	Observational Study	Recruiting	Amsterdam University Medical Centers	NCT06567197
	HDIT-AHSCT	30	Observational Study	Recruiting	Istituto Scientifico Universitario San Raffaele	NCT06267781
	Fludarabine/CY HDIT-AHSCT	200	Phase 1	Recruiting	Petersburg State Pavlov Medical University	NCT05832515
	NM-AHSCT vs. Alemtuzumab/Cladribine/ Ocrelizumab	100	Phase 3	Recruiting	Haukeland University Hospital	NCT03477500
	AHSCT	15	N/A	Recruiting	Sheffield Teaching Hospitals NHS Foundation Trust	NCT06195800
Type 1 diabetes	NM-AHSCT	23	Phase 1/2	Completed	University of São Paulo	NCT00315133
	NM-AHSCT	40	Phase 2	Completed	Shanghai Jiao Tong University School of Medicine	NCT00807651
	NM-AHSCT	13	Phase 2	Completed	The Affiliated Drum Tower Hospital of Nanjing University	NCT01341899
	NM-AHSCT	16	Phase 1/2	Completed	Hospital Universitario Dr. José Eleuterio González	NCT01121029
	AHSCT	100	Phase 1/2	Completed	Stem Cells Arabia	NCT02644759
	UCBT	50	N/A	Recruiting	Children's Hospital of Fudan University	NCT03835312
Crohn's disease	NM-allo-HSCT	9	Phase 1/2	Terminated	Northwestern University	NCT01288053
	NM-AHSCT	24	Phase 1/2	Completed	Northwestern University	NCT00278538
	HDIT-AHSCT	45	Phase 3	Terminated	EBMT	ASTIC NCT00297193
	HSCT	143	Phase 2	Terminated	Fred Hutchinson Cancer Center	NCT01570348
	HDIT-AHSCT + Vedolizumab	50	Phase 2	Recruiting	Icahn School of Medicine at Mount Sinai	NCT03219359
	HDIT-AHSCT	15	Phase 1/2	Recruiting	Cedars-Sinai Medical Center	NCT04224558
	HDIT-AHSCT	20	Phase 1/2	Recruiting	University of Pittsburgh	NCT00692939
Systemic sclerosis	NM-AHSCT	21	Phase 2	Completed	Northwestern University, Feinberg School of Medicine	ASSIST NCT00278525
	HDIT-AHSCT	75	Phase 2/3	Completed	Multicenter study over USA/Canada	SCOT NCT00114530
	NM-AHSCT vs. CY	156	Phase 3	Completed	EBMT	ASTIS ISRCTN54371254
	CY/rATG vs. CY/rATG/ Fludarabine AHSCT	44	Phase 3	Terminated	Northwestern University	NCT01445821
	AHSCT	82	Observational Study	Completed	EBMT ADWP	NISSC-1 NCT02516124
	AHSCT	60	Observational Study	N/A	EBMT ADWP	NISSC-2 NCT03444805
	HDIT-AHSCT	8	Phase 2	Recruiting	University of Pittsburgh	NCT03630211
Systemic lupus erythematosus	NM-AHSCT	9	Phase 2	Completed	National Institutes of Health Clinical Center	NCT00076752
	NM-AHSCT	50	Phase 2	Completed	Northwestern University, Feinberg School of Medicine	NCT00271934

(*continued on next page*)

Table 1 (*continued*)

Conditions	Interventions	Pts	Phases	Status	Institutions	Trial number
	HDIT-AHSCT	7	Phase 1/2	N/A	Charite University, Berlin, Germany	NCT00742300
Systemic sclerosis and Systemic lupus erythematosus	AHSCT	20	Phase 2	Recruiting	Children's Hospital of Philadelphia	NCT05029336

Abbreviations: Pts, patients; AHSCT, Autologous Hematopoietic Stem Cell Transplantation; allo-HSCT, Allogeneic hematopoietic stem cell transplantation; NM-AHSCT, Nonmyeloablative Autologous Hematopoietic Stem Cell Transplantation; HDIT-AHSCT, High-Dose Immunotherapy followed by Autologous Hematopoietic Stem Cell Transplantation; CY, Cyclophosphamide; rATG, Rabbit Antithymocyte Globulin; IVIG, Intravenous immune globulin; EBMT, European Society for Blood and Marrow Transplantation; EBMT ADWP, EBMT Autoimmune Diseases Working Party (ADWP); N/A, Not Applicable.
Notes: "Completed" status means that the clinical study has successfully completed all research steps and objectives according to the predetermined plan. "Terminated" means that the clinical study is prematurely stopped without completing all the predetermined plans.

and are mostly used to treat T1D. Strong preclinical evidence has been obtained in NOD mouse models [147], and phase I clinical studies [148,149] have shown that treating T1D patients with ex vivo expanded autologous $CD4^{+}CD127low/\text{-}CD25^{+}$ polyclonal Treg cells is both safe and effective. Notably, in a proteoglycan-induced arthritis (PGIA) mouse model [150], introducing additional Treg cells during BMT postimmune ablation did not lead to further clinical improvements. Instead, it delayed the reconstitution of graft-derived T-cell compartments, potentially hindering the development of long-term immune tolerance. Therefore, further examination of the combination of HSCT and Treg therapy for the treatment of ADs is needed. Animal studies have shown that in preclinical models of T1D [151], RA [152], and MS [153], antigen-specific Treg cells are more effective than polyclonal Treg cells. Consequently, CAR-Treg cells have also been introduced for treating ADs and have demonstrated effectiveness in EAE mouse models [154] and trinitrobenzene sulfonic acid (TNBS)-induced colitis mouse models [155], providing a strong rationale for clinical studies of CAR-Treg cells. As CAR-T cells and CAR-Treg cells are gradually being applied to treat ADs, it remains unclear whether combining these advanced cellular therapies with traditional transplantation can improve patient outcomes. Therefore, exploring the efficacy of combining cell therapy with HSCT is merited.

In addition to potential treatment-related complications and the recurrence of original ADs, there is also a risk of developing new post-HSCT ADs, termed "secondary" ADs, such as autoimmune thrombocytopenia, acquired hemophilia, autoimmune hemolytic anemia, Evans syndrome, autoimmune thyroiditis, and ulcerative colitis. A 2017 study [94] reported similar incidences, including in patients from the EBMT and CIBMTR databases, where 14 of 281 patients (5 %) developed new ADs during a median follow-up of 6.6 years after auto-HSCT. Preventing graft rejection, GVHD, and "secondary" ADs post-HSCT are now possible through many new methods [135], and both the EBMT and other organizations have recognized the occurrence of "late effects" post-HSCT [156–158], advocating for long-term patient follow-up and optimizing patient selection and transplantation protocols to reduce the risk of post-transplantation complications.

6. Perspectives

The future of HSCT for AD patients largely depends on the "dynamics" of alternative treatment options [4]. While auto-HSCT has been widely used to treat diseases such as MS, SSc, and CD, the available evidence remains relatively limited, and further prospective studies comparing HSCT with continuously evolving modern treatments are necessary to establish the most effective treatment protocols. A key challenge is preserving the therapeutic impact of the conditioning regimen while reducing its toxicity. This is an area that will require significant breakthroughs in the future. Additionally, to optimize safety and patient benefits, efforts should focus on identifying early prognostic biomarkers and using these markers to tailor transplantation techniques and improve patient selection.

CRediT authorship contribution statement

Yuxi Xu: Writing – original draft, Conceptualization. **Xiaoqi Wang:** Writing – original draft. **Ziyi Hu:** Validation, Data curation. **Ruihao Huang:** Formal analysis, Conceptualization. **Guancui Yang:** Formal analysis, Data curation. **Rui Wang:** Investigation. **Shijie Yang:** Investigation. **Liyan Guo:** Investigation. **Qingxiao Song:** Supervision, Funding acquisition. **Jin Wei:** Supervision, Project administration. **Xi Zhang:** Writing – review & editing, Supervision, Funding acquisition.

Ethics requirements

None.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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