

Novel Stem cell therapies in autoimmune diseases: Review of clinical data

Jonathan R.T. Lakey, PhD^{1,2,*}, Yanmin Wang, PhD¹, Ian Jenkins, MBA², Michael Alexander, MSc¹, Chitra Bhakta, MD³, Mike K.S. Chan, PhD^{4,5}, Michelle B.F. Wong, ND, PhD^{4,5}

¹Department of Surgery, University of California Irvine, Irvine, California, USA, 92868

²GATC Health Inc, Suite 660 2030 Main Street, Irvine California USA, 92614

³OC Integrative Medical Center, Newport Beach, California, USA, 92663

⁴European Wellness Academy, Klosterstrasse 205, Edenkoben, Germany, 67480

⁵Baden R&D Laboratories GmbH, Sabine Conrad, Ferdinand-Laselle-Strasse 40 Germany, 72770

Received: January 18, 2024; Accepted: January 19, 2024; Published: February 10, 2024

***Corresponding author:** Jonathan R.T. Lakey, PhD, MSM, Professor Emeritus, Department of Surgery and Biomedical Engineering, University of California Irvine, Irvine CA, 92868; E-mail: jlakey@uci.edu

Abstract

Stem cell therapy is rapidly emerging as a transformative therapeutic approach, particularly in the context of autoimmune diseases that often resist conventional medications. These diseases, characterized by the immune system's paradoxical assault on the body's own tissues, present a significant challenge to medical practitioners and researchers alike. Stem cells possess distinctive attributes, notably their capacity to modulate immunity and rectify immune dysregulation, positioning them at the forefront of immune-based treatments. This review endeavors to succinctly encapsulate the clinical utilization of stem cells in combatting autoimmune diseases.

Introduction

Stem cells represent a class of undifferentiated cells recognized for their exceptional capabilities in self-renewal, regeneration, and specialization into distinct cell lineages, thus enabling the repair and rejuvenation of impaired tissues [1,2]. The exploration of stem cell therapies commenced notably with the inception of bone marrow transplantation in the 1950s, primarily aimed at hematologic disorders [3]. This initial pursuit laid the foundation for an expanded inquiry into the broader applications of stem cells. In recent times, a spotlight has emerged on stem cell therapy, provoking fervent engagement within both research and clinical domains.

Beyond their regenerative potential, stem cells exhibit the remarkable ability to generate peptides with inherent therapeutic promise, fostering opportunities for treating a spectrum of ailments. For instance, European Wellness laboratories developed and manufactured organ-specific mammalian precursor stem cell-derived peptide preparations [4,5,6]. Good clinical outcomes [7,8,9] and safety profile of the peptides have been reported across a wide range of diseases and illnesses where treatment options are limited.

In an era marked by escalating interest in personalized medicine, stem cell therapy stands as a beacon of hope for

individuals plagued by autoimmune diseases that have defied traditional medical interventions. Though the clinical exploration of stem cells is still in its formative stages, the momentum surrounding their potential within autoimmune disease therapy is nothing short of profound. The intent of this comprehensive review paper is to methodically dissect and assess the reservoir of clinical research data germane to the utilization of stem cells in addressing autoimmune diseases. This paper aims to furnish a panoramic snapshot of the existing landscape of research while simultaneously contemplating potential trajectories for future investigation. Notably, this review stands as a pioneering effort, being the inaugural endeavor of its kind to illuminate this burgeoning domain.

Stem Cells and Immune System

There are two primary categories of stem cells: pluripotent stem cells (including embryonic stem cells and induced pluripotent stem cells) and non-embryonic or somatic stem cells, often referred to as "adult" stem cells [11]. Embryonic stem cells exhibit the remarkable ability to differentiate into all cell types found in the adult body. However, their use has been fraught with ethical controversy due to the necessity of destroying human embryos for their extraction [12]. Consequently, the utilization of embryonic stem cells is subject to stringent restrictions. In contrast, induced pluripotent stem cells are generated by reprogramming adult cells, sidestepping the ethical concerns associated with embryonic stem cells. Nevertheless, their application is not without limitations. These cells may retain some features of their original cell type, potentially leading to genetic mutations, tumor formation, or other undesired outcomes [13].

Adult stem cells, sourced from a variety of body tissues such as bone marrow, peripheral blood, umbilical cord blood and tissue, adipose tissue, skin, neurons, and muscle, constitute the other major category. Stem cells possess a repertoire of distinctive attributes that render them intriguing candidates for immune-based treatments. One of their hallmarks is the inherent ability

to fine-tune and recalibrate the immune response [14,15]. By modulating immune cell activity and communication, stem cells hold the potential to counteract the immune system's misdirected attacks, offering a novel strategy for restoring harmony within the body's defenses [14,15]. Moreover, stem cells exhibit an unparalleled versatility in their differentiation capabilities [1], enabling them to assume multiple cellular identities as the situation demands. This adaptability positions them as agents of repair, capable of mending the tissue damage wrought by autoimmune onslaughts.

The administration of stem cell-derived peptides stimulates peptide production or restores normal signaling patterns, enhancing the strength of signals received by cells. Prior research has demonstrated the effectiveness of peptide therapy in reducing T cell activation and improving autoimmune responses [16,17].

Stem cell transplantation generally follows one of two methods [18]: autologous infusion, wherein stem cells are harvested from the patient being treated, and allogeneic infusion, where stem cells are obtained from a genetically distinct individual. Autologous stem cell infusion has gained widespread acceptance due to perceived benefits such as curbing early intra-graft inflammation and reducing the risk of acute rejection [18]. On the other hand, the distinctive attributes of stem cells, coupled with their interaction with the immune system, make allogeneic use feasible [14,15]. Allogeneic infusion holds promise for harnessing the regenerative capacities of cells from healthy donors. This dual approach showcases the dynamic potential of stem cell transplantation, offering a spectrum of strategies tailored to specific clinical contexts.

Autoimmune Diseases and Stem Cell Therapy

Autoimmune diseases constitute a diverse group of disorders wherein the body's immune system, typically a defender against external threats, erroneously targets its own tissues. This results in chronic inflammation and tissue damage across various organ systems. In Western countries, autoimmune diseases affect around 10% of the population [19], and the incidence has been increasing. While current treatments have made significant strides in managing these conditions, they are not without limitations and challenges.

In current treatment guidelines, hematopoietic stem cells (HSCs) transplant has been considered as a therapeutic option at second line or beyond for patients with severe autoimmune diseases progressing (level II) [20], while mesenchymal stem cells (MSCs) have also been recommended as potentially effective treatment for some autoimmune diseases [21]. Clinical data have been reported.

Multiple Sclerosis (MS), an emblematic autoimmune disease, is characterized by demyelination of nerve fibers in the central nervous system. Current treatments for MS encompass disease-modifying therapies that seek to mitigate relapses, manage symptoms, and slow disease progression. These therapies, ranging from interferons to monoclonal antibodies, aim to temper immune responses and minimize neural damage. However, they

often come with potential side effects, and not all patients respond equally. Additionally, the challenge of accessing and maintaining these therapies, especially for patients in underserved regions, can impede their effectiveness.

Meta-analysis [22] has demonstrated that autologous HSC transplant can induce long-term remissions for MS patients with a high degree of safety. HSC treatment has proven effective in achieving remission of relapses in MS patients unresponsive to conventional treatments [23]. Multicenter clinical studies and meta-analysis [24,25] have shown that autologous HSC transplant is associated with a decreased Expanded Disability Status Scale (EDSS) score or a lower progression rate of MS. Somani et al. [26] evaluated 15 studies including 764 autologous HSC transplanted patients suffered from MS. The proportion of no evidence of disease activity patients was 83% at 2 years and 67% at 5 years.

In an open-label prospective phase I/IIa clinical study [27], autologous bone marrow-derived mesenchymal stromal cells followed by mesenchymal stromal cells conditioned media were used in 10 MS patients who failed conventional therapy. The treatment protocol was well-tolerated, and there was an overall trend of improvement in clinical, cognitive, ophthalmology, and radiological tests, as well as EDSS scores. In a double-blind, randomized controlled trial [28], intrathecal (IT) and intravenous (IV) infusion of autologous MSC were performed in patients with progressive MS. Results showed that both IT and IV routes achieved predefined endpoints, while IT was more effective. Riordan et al. [29] reported improved symptoms and quality of life in MS patients after MSC IV infusion.

Rheumatoid Arthritis (RA) is a chronic autoimmune affliction typified by joint inflammation, pain, and progressive deformity. The therapeutic landscape for RA has evolved considerably, with treatments spanning nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and biologic agents. These interventions, such as TNF-alpha inhibitors, seek to quell inflammatory cascades and thwart joint deterioration. However, not all patients experience sustained benefits, and long-term use can be associated with risks such as increased susceptibility to infections. Furthermore, the high costs of biologic therapies can limit accessibility for many individuals.

Snowden et al. [30] reported that autologous HSCT is safe and effective in 73 patients with severe, resistant RA, achieving significant responses in most patients. In addition, both autologous bone marrow derived MSC and allogeneic adipose tissue derived MSC were reported as well tolerated and effective in RA patients. Ra et al. [31] investigated IV and/or intraarticular (IA) infusion of autologous adipose tissue derived MSC in patients with RA and found that the treatments were clinically effective without serious adverse events. Similarly, Vij et al. [32] conducted an open-label clinical trial and reported that a single IV administration of autologous adipose tissue MSC is safe and efficacious for improvement in joint function in patients with active RA. Shandmanfar et al. [33] and Ghoryani et al. [34] completed clinical trials on RA patients with IA or IV injection of autologous bone marrow derived MSC respectively.

Both of their findings showed safety and efficiency of the MSC therapy. Additionally, umbilical cord MSC treatment has also been reported as a safe, effective, and feasible therapeutic option for RA patients. In a study involving 64 RA patients [35], after IV infusion of MSCs at 1 year and 3 years, blood routine, liver and kidney function, and immunoglobulin examinations remained within the normal range, while health index and joint function index decreased compared to baseline.

Systemic lupus erythematosus(SLE) manifests as a complex autoimmune disorder that can impact multiple organs, including the skin, joints, kidneys, and heart. Current treatments for SLE encompass a range of medications, including corticosteroids, antimalarials, and immunosuppressive agents like mycophenolate and cyclophosphamide. These approaches are designed to modulate the immune response and manage the diverse clinical manifestations of the disease, but achieving consistent disease control remains a challenge. The heterogeneity of SLE makes developing tailored treatment plans difficult, and many patients continue to grapple with unpredictable disease courses.

Marmont et al. [36] documented a notable case of a female patient with longstanding and severe SLE who exhibited substantial clinical enhancements following autologous HSC treatment. In a study involving 24 SLE patients, Leng et al. [37] showcased an impressive progression-free survival rate of 86% following HSC implant. Similarly, another investigation [38] observed a noteworthy long-term reduction in proteinuria levels, nearly restoring them to a normal range.

MSC also played a positive role in the treatment of SLE. In a multicenter clinical study enrolling 40 patients with active SLE, Wang et al. [39] showed that infusion of allogeneic umbilical cord MSC significantly improved clinical indices. Liang et al. [40] found improvements of skin complications, arthritis, refractory hypertension, and renal dysfunction in SLE patients after MSC treatment.

Psoriasis is a skin-centric autoimmune disease marked by rapid skin cell turnover, leading to scaly patches and plaques. Current treatments encompass topical agents, phototherapy, and systemic medications like biologic agents that specifically target immune pathways involved in the disease. Topical treatments may offer limited relief for those with widespread disease, while systemic therapies can have potential risks like immune suppression and interactions with other medications.

Kaffenberger et al. [41] demonstrated in their study that patients suffering from psoriasis attained extended periods of remission following allogeneic HSC treatment, while it is likely to recur after autologous HSC transplantation. In a separate research effort by Chen et al. [42], favorable outcomes were observed in the treatment of psoriasis using umbilical cord derived MSC, as evident in two case reports. Another study, designed as a single-arm investigation, involved 17 patients with psoriasis who underwent umbilical cord-derived MSC therapy [43]. Notably, six months post-treatment, a substantial 47% of patients exhibited an improvement of at least 40% in their Psoriasis Area and

Severity Index, while 17.6% displayed no signs of disease or minimal disease according to the Physicians' Global Assessment.

Type 1 Diabetes Mellitus(T1DM) arises from immune-mediated destruction of insulin-producing cells in the pancreas. Insulin replacement therapy is the cornerstone of treatment, supplemented by continuous glucose monitoring and advances like insulin pumps. While insulin replacement is essential, it doesn't address the underlying immune attack. Attempts at immunomodulation to halt disease progression can be complex due to the delicate balance required to avoid compromising the overall immune system.

A meta-analysis [44] revealed that HSC therapy led to satisfactory therapeutic outcome for T1DM. Thakkar et al. [45] conducted a prospective trial for patients with T1DM and found that autologous bone marrow HSC plus adipose-derived insulin-secreting mesenchymal stromal cells offered satisfactory long-term hyperglycemic control. In a study by Snarski et al. [46], 8 patients with newly diagnosed T1DM underwent bone marrow HSC transplantation. Following treatment, all patients were less dependent on exogenous insulin and exhibited lower HbA1c levels. Li et al. [47] infused HSC in patients with T1DM who developed symptoms within 12 months of diagnosis. Over 31 to 54 months, 11 out of 15 patients had decreased HbA1c and increased C-peptide concentrations, along with reduced doses of insulin for glycemic control, indicating an improvement of beta-cell function. Mesples et al. [48] reported a novel approach for autologous bone marrow HSC transplantation in a cohort of 6 young diabetic patients. At 6 months after treatment, 5 patients demonstrated decreased blood glucose and HbA1C levels along with improved values of islet cell antibodies, glutamic acid-decarboxylase, and tyrosine phosphatase-related islet antigen 2 antibodies, and no complications occurred during follow-up.

In an RCT [49], an IV injection of autologous bone marrow MSC or placebo was performed in 21 patients with newly diagnosed T1DM. The results indicated that patients who underwent MSC treatment showed improved levels of C-peptide and HbA1c. Similarly, in a study by Carlsson et al. [50], patients with new-onset T1DM received IV autologous MSC treatment and were followed up for 1 year. Compared to the control group, their beta-cell functions were preserved.

Inflammatory Bowel Disease(IBM), encompassing Crohn's disease (CD) and ulcerative colitis, leads to chronic inflammation of the gastrointestinal tract. Current treatments include anti-inflammatory drugs, immune suppressants, and biologic therapies that target specific immune molecules to temper the gut's immune response. Balancing the risks of immunosuppression with the need to control inflammation presents an ongoing challenge.

Previous studies have indicated unsatisfactory safety and efficacy of HSC therapy in CD. The randomized controlled trial ASTIC [51], focusing on refractory CD, reported limited achievement of study endpoints after HSC treatment, along with the occurrence of serious adverse events. In a single-center study involving 29 CD patients [52], long-term follow-up revealed drug-

free and endoscopic remission in 61% at one year, diminishing to 15% by the fifth year. A recent retrospective study [53] with 82 patients showed HSC transplantation leading to clinical remission in 43% at one year, but 73% required reintroduction of CD treatment.

In contrast to HSC, clinical studies have reported that MSC treatment caused clinical improvements in CD. In a randomized controlled clinical trial conducted by Zhang et al. [54], 82 patients with CD received intravenous umbilical cord MSCs. Following treatment, improvements were observed in CD symptoms, CD activity index, Harvey-Bradshaw index, and corticosteroid dosage, with no serious adverse events. Forbes et al. [55] conducted a phase 2 study and demonstrated that the infusion of allogeneic MSCs improved CD activity index and CD endoscopic index of severity scores in patients with luminal CD refractory to biologic therapy. In a phase 3 double-blind randomized controlled study (ADMIRE-CD) [56] enrolling 212 patients, allogeneic adipose-derived MSCs exhibited good tolerance and sustained clinical remission for up to 104 weeks in perianal fistulizing Crohn's disease. A retrospective study [57] indicated that allogeneic bone marrow-derived MSCs ameliorated fistulas in CD patients, contributing to the recovery of patients' quality of life in a 4-year follow-up.

Autoimmune liver disease (AILD) involves inflammation of the liver due to an autoimmune attack. It includes autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis. Treatment involves corticosteroids and immune suppressants to suppress the immune response and preserve liver function. Prolonged use of immune suppressants raises concerns about potential side effects such as increased infection susceptibility and bone density loss. Additionally, not all patients respond equally to these medications, highlighting the need for personalized treatment approaches.

Investigations have shown that stem cell therapy in AILDs is both safe and effective. Calorie et al. [58] documented a case involving a patient with autoimmune hepatitis who underwent allogeneic HSC treatment. After the treatment, the patient's antinuclear and anti-smooth muscle autoantibodies yielded negative test results.

In a study by Wang et al. [59], individuals diagnosed with primary biliary cholangitis received intravenous administration of MSC. This intervention resulted in a noteworthy reduction in serum alkaline phosphatase (ALP) and gamma-glut amytransferase (GGT) levels following the treatment. Another study [60] came to a similar conclusion that after allogeneic bone marrow derived MSC transplantation, patients with ursodeoxycholic acid (UDCA)-resistant primary biliary cirrhosis exhibited improved quality of life and increased levels of hepatic function. The optimal therapeutic outcome was acquired in 3 to 6 months and could be maintained for 12 months after MSC transplantation.

Sjögren's Syndrome leads to dryness of the eyes and mouth due to immune-mediated damage to exocrine glands. Current

treatments focus on managing symptoms and preventing complications. However, addressing the underlying immune dysfunction remains a challenge. Developing therapies that target the immune component without compromising the body's defense mechanisms presents a complex task.

Xu et al. [61] conducted a study involving 24 patients diagnosed with Sjögren's syndrome, administering allogeneic umbilical cord MSC. This intervention yielded noteworthy enhancements in clinical manifestations, Sjögren's Syndrome Disease Activity Index, Visual Analogue Scale scores, and salivary flow rates. Notably, no adverse effects were reported.

There are some other types of autoimmune diseases such as Graves' Disease, Hashimoto's Thyroiditis, and Addison's Disease. However, currently stem cell therapy has not been used on them.

Challenges and Future Directions

The use of stem cells is still in its early stages, and many challenges and limitations need to be addressed before stem cell therapy can become a more widely accepted treatment. Issues such as ensuring the precise targeting of aberrant immune responses, optimizing the safety profile of stem cell interventions, and defining standardized protocols pose significant hurdles. Moreover, a thorough examination is required to assess the long-term effectiveness and sustainability of therapeutic outcomes. Future directions involve advancing our understanding of the intricate interplay between stem cells and the immune system, tailoring therapies to individual patient profiles, and harnessing emerging technologies for enhanced precision. Overcoming these challenges and navigating future avenues will be pivotal in unlocking the full therapeutic potential of stem cells in the realm of autoimmune diseases.

Conclusion

Despite the challenges and limitations inherent in stem cell therapy, it has demonstrated a commendable safety profile and efficacy in addressing autoimmune diseases. While additional research is imperative to comprehensively uncover the extent of stem cells' potential, existing evidence substantiates their utility as an asset in the management of numerous conditions. The ongoing exploration of this field bears the potential to propel the enhancement of patients' health and well-being to new horizons.

References

1. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. *Stem Cell Res Ther.* 2019; 10.
2. Rajabzadeh N, Fathi E, Farahzadi R. Stem cell-based regenerative medicine. *Stem Cell Investig.* 2019; 6.
3. Juric MK, Ghimire S, Ogonek J, et al. Milestones of Hematopoietic Stem Cell Transplantation - From First Human Studies to Current Developments. *Front Immunol.* 2016; 7: 470..
4. Wells A, Good A, Damyar K, et al. Mass Spectrometry Analysis of Novel Stem Cell-Derived Peptides. *Am J Biomed Sci Res.* 2022; 16: 232-239.
5. Klokol D, Tulina D, Teppone M, et al. Application of Cell Extracts from Skin, Placenta, Mesenchyme with Collagen and Elastin in Aesthetic

- Dermatology and Skin Revitalization: Evaluation of Outcomes in Cohort Study. *Am J Adv Drug Deliv*. 2016; 4: 69–77.
6. Chan MKS, Wong M, Beguin A, et al. Efficacy of the MFIII placenta extracts softgels supplementation: a randomized double-blind placebo-controlled study. *Basic Research Journal of Medicine and Clinical Sciences*. 2016; 5: 86–95.
 7. Klokol D, Chan MKS, Wong MBF. European Wellness – The Evidenced Rationale behind the Biological Medicine: *Ad Astra Per Aspera*. *J Pharm Biomed Sci*. 2017; 7: 19–22.
 8. Klokol D, Nallenthiran L, Chan MKS, et al. Cell Therapy As The Main Stratagem Of Anti-aging And Regenerative Medicine. *Europ J Pharm Med Res*. 2019; 6: 295–299.
 9. Moya R, Chan MKS, Wong MBF, et al. Active Specific Immunotherapy (ASI) in Cancer Treatment: Five Case Reports. *J Cancer Sci Ther*. 2019; 11: 256–259.
 10. Lakey JRT, Cox CTD, Whaley D, et al. ORGAN-Specific Peptide Canine Safety Study. *Am J Biomed Sci Res*. 2022; 16: 345–349.
 11. National Institute of Health. Stem Cell Basics. Accessed Dec 22, 2023
 12. Lo B, Parham L. Ethical Issues in Stem Cell Research. *Endocr Rev*. 2009; 30: 204–213.
 13. Yamamoto T, Sato Y, Yasuda S, et al. Correlation Between Genetic Abnormalities in Induced Pluripotent Stem Cell-Derivatives and Abnormal Tissue Formation in Tumorigenicity Tests. *Stem Cells Transl Med*. 2022; 11: 527–538.
 14. Wang Y, Chen X, Cao W, Shi Y. Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications. *Nat Immunol*. 2014; 15: 1009–1016.
 15. Gao F, Chiu SM, Motan DAL, et al. Mesenchymal stem cells and immunomodulation: current status and future prospects. *Cell Death Dis*. 2016; 7: e2062.
 16. Lakey JRT, Wells A, Good A, et al. Protective Effects of Stem Cell-Derived Peptides in Preventing Autoimmune Diabetes in the Non-Diabetic Mouse Model. *Am J Biomed Sci Res*. 2022; 16: 496–502. doi:10.34297/AJBSR.2022.16.002264.
 17. Moya R, Chan MKS, Wong MBF, Klokol D. Integration of active specific immunotherapy and cell therapy into the protocols of biomedical management of interstitial pneumonia with autoimmune features – A case study. *Clinical and Medical Reports*. 2020; 3: 1–5.
 18. Alagesan S, Griffin MD. Autologous and allogeneic mesenchymal stem cells in organ transplantation: what do we know about their safety and efficacy? *Curr Opin Organ Transplant*. 2014; 19: 65–72.
 19. Conrad N, Misra S, Verbakel JY, et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. *Lancet*. 2023; 401: 1878–1890.
 20. Snowden JA, Saccardi R, Allez M, et al. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2012; 47: 770–790.
 21. Freedman MS, Bar-Or A, Atkins HL, et al. The therapeutic potential of mesenchymal stem cell transplantation as a treatment for multiple sclerosis: consensus report of the International MSCT Study Group. *Mult Scler*. 2010; 16: 503–510.
 22. Ge F, Lin H, Li Z, Chang T. Efficacy and safety of autologous hematopoietic stem-cell transplantation in multiple sclerosis: a systematic review and meta-analysis. *Neurol Sci*. 2019; 40: 479–487.
 23. Xu J, Ji BX, Su L, Dong HQ, Sun XJ, Liu CY. Clinical outcomes after autologous haematopoietic stem cell transplantation in patients with progressive multiple sclerosis. *Chin Med J (Engl)*. 2006; 119: 1851–1855.
 24. Nabizadeh F, Pirahesh K, Rafiei N, et al. Autologous Hematopoietic Stem-Cell Transplantation in Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Neurol Ther*. 2022; 11: 1553–1569.
 25. Muraro PA, Pasquini M, Atkins HL, et al. Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis. *JAMA Neurol*. 2017; 74: 459–469.
 26. Sormani MP, Muraro PA, Schiavetti I, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: A meta-analysis. *Neurology*. 2017; 88: 2115–2122.
 27. Dabhour S, Jamali F, Alhatab D, et al. Mesenchymal stem cells and conditioned media in the treatment of multiple sclerosis patients: Clinical, ophthalmological and radiological assessments of safety and efficacy. *CNS Neurosci Ther*. 2017; 23: 866–874.
 28. Petrou P, Kassis I, Levin N, et al. Beneficial effects of autologous mesenchymal stem cell transplantation in active progressive multiple sclerosis. *Brain*. 2020; 143: 3574–3588.
 29. Riordan NH, Morales I, Fernandez G, et al. Clinical feasibility of umbilical cord tissue-derived mesenchymal stem cells in the treatment of multiple sclerosis. *J Transl Med*. 2018; 16: 57.
 30. Snowden J, Passweg J, Moore JJ, et al. Autologous hemopoietic stem cell transplantation in severe rheumatoid arthritis: A report from the EBMT and ABMTR. *J Rheumatol*. 2004; 31: 482–488.
 31. Ra JC, Shin IS, Kim SH, et al. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. *Stem Cells Dev*. 2011; 20: 1297–1308.
 32. Vij R, Stebbings KA, Kim H, Park H, Chang D. Safety and efficacy of autologous, adipose-derived mesenchymal stem cells in patients with rheumatoid arthritis: a phase I/IIa, open-label, non-randomized pilot trial. *Stem Cell Res Ther*. 2022; 13: 88.
 33. Shadmanfar S, Labibzadeh N, Emadedin M, et al. Intra-articular knee implantation of autologous bone marrow-derived mesenchymal stromal cells in rheumatoid arthritis patients with knee involvement: Results of a randomized, triple-blind, placebo-controlled phase 1/2 clinical trial. *Cytotherapy*. 2018; 20: 499–506.
 34. Ghoryani M, Shariati-Sarabi Z, Tavakkol-Afshari J, Ghasemi A, et al. Amelioration of clinical symptoms of patients with refractory rheumatoid arthritis following treatment with autologous bone marrow-derived mesenchymal stem cells: A successful clinical trial in Iran. *Biomed Pharmacother*. 2019; 109: 1834–1840.
 35. Wang L, Huang S, Li S, et al. Efficacy and Safety of Umbilical Cord Mesenchymal Stem Cell Therapy for Rheumatoid Arthritis Patients: A Prospective Phase I/II Study. *Drug Des Devel Ther*. 2019; 13: 4331–4340.
 36. Marmont AM, Van Lint MT, Gualandi F, Bacigalupo A. Autologous marrow stem cell transplantation for severe systemic lupus erythematosus of long duration. *Lupus*. 1997; 6: 545–548.
 37. Leng XM, Jiang Y, Zhou DB, et al. Good outcome of severe lupus

- patients with high-dose immunosuppressive therapy and autologous peripheral blood stem cell transplantation: a 10-year follow-up study. *Clin Exp Rheumatol*. 2017; 35: 494–499.
38. Cao C, Wang M, Sun J, et al. Autologous peripheral blood haematopoietic stem cell transplantation for systemic lupus erythematosus: the observation of long-term outcomes in a Chinese centre. *Clin Exp Rheumatol*. 2017; 35: 500–507.
39. Wang D, Li J, Zhang Y, et al. Umbilical cord mesenchymal stem cell transplantation in active and refractory systemic lupus erythematosus: a multicenter clinical study. *Arthritis Res Ther*. 2014; 16: R79.
40. Liang J, Zhang H, Hua B, et al. Allogeneic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study. *Ann Rheum Dis*. 2010; 69: 1423–1429.
41. Kaffenberger BH, Wong HK, Jarjour W, Andritsos LA. Remission of psoriasis after allogeneic, but not autologous, hematopoietic stem-cell transplantation. *J Am Acad Dermatol*. 2013; 68: 489–492.
42. Chen H, Niu JW, Ning HM, et al. Treatment of Psoriasis with Mesenchymal Stem Cells. *Am J Med*. 2016; 129: e13–e14.
43. Cheng L, Wang S, Peng C, et al. Human umbilical cord mesenchymal stem cells for psoriasis: a phase 1/2a, single-arm study. *Signal Transduct Target Ther*. 2022; 7: 263.
44. El-Badawy A, El-Badri N. Clinical Efficacy of Stem Cell Therapy for Diabetes Mellitus: A Meta-Analysis. *PLoS One*. 2016; 11: e0151938.
45. Thakkar UG, Trivedi HL, Vanikar AV, Dave SD. Insulin-secreting adipose-derived mesenchymal stromal cells with bone marrow-derived hematopoietic stem cells from autologous and allogeneic sources for type 1 diabetes mellitus. *Cytherapy*. 2015; 17: 940–947.
46. Snarski E, Milczarczyk A, Torosian T, et al. Independence of exogenous insulin following immunoablation and stem cell reconstitution in newly diagnosed diabetes type I. *Bone Marrow Transplant*. 2011; 46: 562–566.
47. Li L, Shen S, Ouyang J, et al. Autologous hematopoietic stem cell transplantation modulates immunocompetent cells and improves β -cell function in Chinese patients with new onset of type 1 diabetes. *J Clin Endocrinol Metab*. 2012; 97: 1729–1736.
48. Mesples AD, Cox DCT, Lundy HD, et al. Monitoring of Autoantibodies Following Autologous Hematopoietic Stem Cell Transplantation in 6 Children with Recently Diagnosed Type 1 Diabetes Mellitus. *Med Sci Monit*. 2023; 29: e938979 (2023).
49. Izadi M, Nejad ASH, Moazenchi M, et al. Mesenchymal stem cell transplantation in newly diagnosed type-1 diabetes patients: a phase I/II randomized placebo-controlled clinical trial. *Stem Cell Res Ther*. 2022; 13: 264.
50. Carlsson PO, Schwarcz E, Korsgren O, Le Blanc K. Preserved β -cell function in type 1 diabetes by mesenchymal stromal cells. *Diabetes*. 2015; 64: 587–592.
51. Hawkey CJ, Allez M, Clark MM, et al. Autologous Hematopoietic Stem Cell Transplantation for Refractory Crohn Disease: A Randomized Clinical Trial. *JAMA*. 2015; 314: 2524–2534.
52. López-García A, Rovira M, Jauregui-Amezaga A, et al. Autologous Haematopoietic Stem Cell Transplantation for Refractory Crohn's Disease: Efficacy in a Single-Centre Cohort. *J Crohns Colitis*. 2017; 11: 1161–1168.
53. Brierley CK, Castilla-Llorente C, Labopin M, et al. Autologous Haematopoietic Stem Cell Transplantation for Crohn's Disease: A Retrospective Survey of Long-term Outcomes From the European Society for Blood and Marrow Transplantation. *J Crohns Colitis*. 2018; 12: 1097–1103.
54. Zhang J, Lv S, Liu X, Song B, Shi L. Umbilical Cord Mesenchymal Stem Cell Treatment for Crohn's Disease: A Randomized Controlled Clinical Trial. *Gut Liver*. 2018; 12: 73–78.
55. Forbes GM, Sturm MJ, Leong RW, et al. A phase 2 study of allogeneic mesenchymal stromal cells for luminal Crohn's disease refractory to biologic therapy. *Clin Gastroenterol Hepatol*. 2014; 12: 64–71.
56. Garcia-Olmo D, Gilaberte I, Binek M, et al. Follow-up Study to Evaluate the Long-term Safety and Efficacy of Darvadstrocel (Mesenchymal Stem Cell Treatment) in Patients With Perianal Fistulizing Crohn's Disease: ADMIRE-CD Phase 3 Randomized Controlled Trial. *Dis Colon Rectum*. 2022; 65: 713–720.
57. Barnhoorn MC, Wasser MNJM, Roelofs H, et al. Long-term Evaluation of Allogeneic Bone Marrow-derived Mesenchymal Stromal Cell Therapy for Crohn's Disease Perianal Fistulas. *J Crohns Colitis*. 2020; 14: 64–70.
58. Calore E, Marzollo A, Cananzi M, et al. Haploidentical stem cell transplantation cures autoimmune hepatitis and cerebrovascular disease in a patient with sickle cell disease. *Bone Marrow Transplant*. 2018; 53: 644–646.
59. Wang L, Li J, Liu H, et al. Pilot study of umbilical cord-derived mesenchymal stem cell transfusion in patients with primary biliary cirrhosis. *J Gastroenterol Hepatol*. 2013; 28 Suppl 1: 85–92.
60. Wang L, Han Q, Chen H, et al. Allogeneic bone marrow mesenchymal stem cell transplantation in patients with UDCA-resistant primary biliary cirrhosis. *Stem Cells Dev*. 2014; 23: 2482–2489.
61. Xu J, Wang D, Liu D, et al. Allogeneic mesenchymal stem cell treatment alleviates experimental and clinical Sjögren syndrome. *Blood*. 2012; 120: 3142–3151.