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CONCISE REVIEW

STEM CELLS TRANSLATIONAL MEDICINE

Advances in mesenchymal stem cell therapy for immune and inflammatory diseases: Use of cell-free products and human pluripotent stem cell-derived mesenchymal stem cells

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Abstract

Mesenchymal stem cell therapy (MSCT) for immune and inflammatory diseases continues to be popular based on progressive accumulation of preclinical mechanistic evidence. This has led to further expansion in clinical indications from graft rejection, autoimmune diseases, and osteoarthritis, to inflammatory liver and pulmonary diseases including COVID-19. A clear trend is the shift from using autologous to allogeneic MSCs, which can be immediately available as off-the-shelf products. In addition, new products such as cell-free exosomes and human pluripotent stem cell (hPSC)-derived MSCs are exciting developments to further prevalent use. Increasing numbers of trials have now published results in which safety of MSCT has been largely demonstrated. While reports of therapeutic endpoints are still emerging, efficacy can be seen for specific indications—including graft-vs-host-disease, strongly Th17-mediated autoimmune diseases, and osteoarthritis—which are more robustly supported by mechanistic preclinical evidence. In this review, we update and discuss outcomes in current MSCT clinical trials for immune and inflammatory disease, as well as new innovation and emerging trends in the field.

KEYWORDS

autoimmune diseases, clinical trials, exosomes, extracellular vesicles, graft rejection, human, human pluripotent stem cells, liver cirrhosis, mesenchymal stem/stromal cell therapy, organ transplantation, pulmonary inflammation

Significance statement

Mesenchymal stem cell therapy (MSCT) for immune and inflammatory diseases continues to be popular, leading to further expansion of clinical indications. A clear trend is the shift from using autologous to allogeneic MSCs, and new products such as cell-free exosomes and human pluripotent stem cell (hPSC)-derived MSCs, all of which can be immediately available as off-the-shelf products. While safety of MSCT is well demonstrated, reports of therapeutic endpoints are still emerging with some trends for specific diseases, which are updated and discussed in this article.

1 | INTRODUCTION

Mesenchymal stem/stromal cells (MSCs) are multipotent progenitor cells capable of supporting hematopoiesis and differentiation into the multiple mesodermal lineages of osteoblasts, chondrocytes, and adipocytes.[1-3] First found in the bone marrow (BM), MSCs have been isolated from numerous organs/tissues over the past several decades, but in vivo identity remains somewhat elusive, with increasing evidence for a perivascular origin.[4-6] An unexpected function of MSCs—especially prominent with human sources—is its strong immunomodulatory properties, which have been best delineated toward CD4 cells but also well characterized against a variety of myeloid and innate leukocytes, including dendritic cells, monocytes, and macrophages.[7-9] While initial preclinical data of MSC therapeutic efficacy were mainly focused on regenerative and differentiation capacity, it quickly became apparent that the immunomodulatory properties not only are clinically relevant but allow for allogeneic, unmatched use of these progenitor cells. The application of MSCs toward immune and inflammatory diseases rapidly ensued, with a doubling of clinical trials for these conditions within the past 5 years.[10] Moreover, discoveries of new mechanisms and new products—including using MSC-derived products and human pluripotent stem cell (hPSC) including embryonic stem cell (ESC) and induced PSC (iPSC)-derived MSCs—as well as emerging diseases such as COVID-19 has continued to widen the clinical application of MSC immunomodulation.[11] We therefore review the current status of clinical trials using MSC therapy (MSCT) for inflammatory or immune-related diseases and discuss new advances in the field.

2 | BRIEF SUMMARY ON PRECLINICAL EVIDENCE OF MSC IMMUNOMODULATORY MECHANISMS

The immunomodulatory properties of MSCs are well demonstrated toward both lymphoid and myeloid cells, with increasing accumulation of mechanistic evidence (Figure 1). MSC immune functions have been best documented against CD4 T lymphocytes, a critical leukocyte population in orchestrating overall immune responses. Numerous reports have shown that MSCs modulate these adaptive cells from an inflammatory milieu filled predominantly with effector T cells to a regulatory T (Treg)-rich microenvironment largely through paracrine factors, most commonly through transforming growth factor beta (TGF-β), hepatocyte growth factor (HGF)[12] prostaglandin E_2 (PGE_2),[13] nitric oxide (NO), and indoleamine 2,3-dioxygenase (IDO).[8,14-16] While a few studies found cell-cell contact involved in MSC-T cell immunomodulation,[17] this mechanism is more prominent in MSC-NK interactions, involving downregulation of activating NK receptors

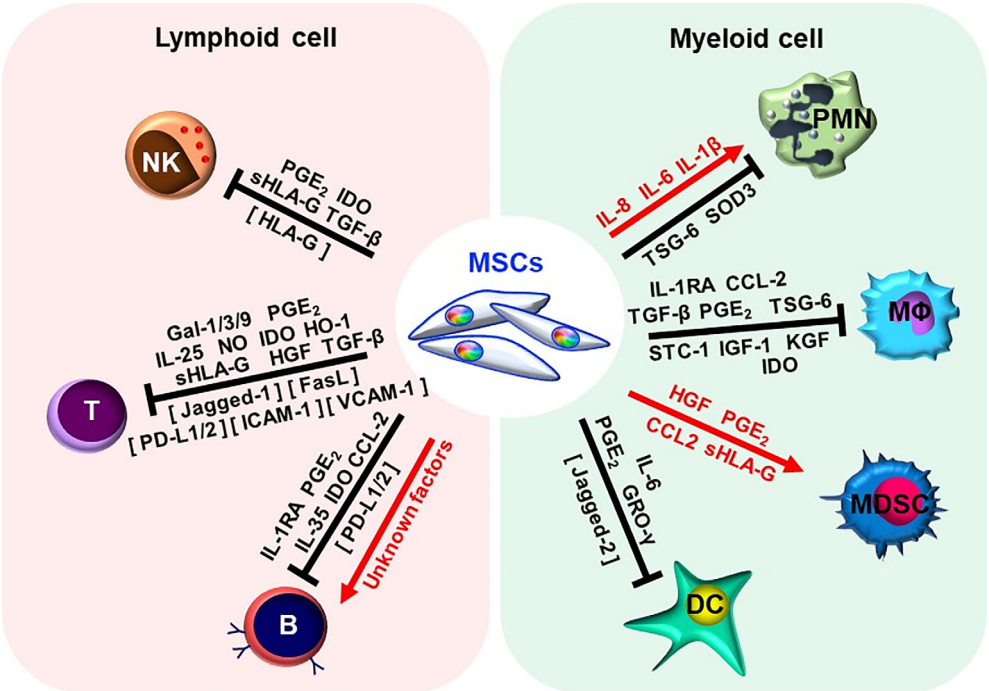

FIGURE 1 Mechanisms of mesenchymal stem cell (MSC) immunomodulation toward lymphoid and myeloid cells as evidenced in preclinical in vivo studies. NK, natural killer cell; PMN, polymorphonuclear neutrophil; MΦ, macrophage; MDSC, myeloid-derived suppressor cell; DC, dendritic cell; PGE_2, prostaglandin E2; IDO, Indoleamine 2,3-dioxygenase; HLA-G, human leukocyte antigen-G; TGF-β, transforming growth factor beta; Gal, galectin; IL, Interleukin; NO, nitric oxide; HO-1, heme oxygenase-1; HGF, hepatocyte growth factor; PD-L, programmed death-ligand; IL-1RA, interleukin-1 receptor antagonist; CCL2, chemokine ligand 2; TSG-6, TNF-stimulated gene 6 protein; SOD3, superoxide dismutase 3; SCT-1, stanniocalcin-1; IGF-1, insulin-like growth factor-1; KGF, keratinocyte growth factor; GRO-γ, growth related oncogene γ. Cell-contact factors are denoted in brackets

such as KIR, NKp30, NKp44 and NKG2D through MSC-expressed surface and soluble HLA-G, a non-classical MHC class I molecule important in fetal-maternal immunomodulation.[18,19] Interestingly, immunomodulatory paracrine factors such as PGE_2 and IDO inducible by inflammatory signals including IFN-γ and IL-1β are prominent in MSC interactions across leukocyte subpopulations including all lymphoid cells including T cells, NKs,[20] and B cells in which IL-10-expressing regulatory B cells are expanded.[21,22] Reports are most scarce for MSC-B cell interactions, but most demonstrate suppression of B cell proliferation, differentiation, and antibody production[23-29]; our recent report found that MSC-B cell interactions may be more complex than previously thought due to MSC source-specific differences in expression of relevant factors.[30] Such information on tissue-specific MSC properties may provide insights which could prove relevant for clinical application.[11,31]

The broad reach of MSC immunomodulation is best exemplified by interactions with myeloid cells, which are much more heterogenous than lymphoid cells. Among early reports of MSC modulation are studies on dendritic cells (DCs)—professional antigen-presenting cells that initiate T cell response—in which MSC paracrine factors including IL-6,[32] PGE_2,[33] and growth-regulated oncogene (GRO)-γ,[34] as well as cell-cell contact through Jagged-2[35], suppress maturation and lead to the development of regulatory DCs, which are more immature and tolerogenic. MSCs have also been seen to inhibit activation of macrophages and/or induce polarization into an alternative M2 phenotype which are critical in resolving inflammation, with data indicating involvement of paracrine factors including IL-1RA,[36] PGE_2,[37] and IDO.[10,38,39] MSCs also expand myeloid-derived suppressor cells (MDSCs), a heterogeneous myeloid population defined by their tolerogenic function, through secreting HGF,[40] CCL2,[41] PGE2,[42] and HLA-G.[43] MSC interactions with granulocytes are best reported for polymorphonuclear neutrophils (PMNs), but results are somewhat variable possibly due to differences in MSC tissue source. Both BMMSCs and PMSCs prevented PMN apoptosis via IL-6 secretion,[44,45] but BMMSCs suppress PMN recruitment via TNF-stimulated gene 6 protein (TSG-6) secretion,[46] and inhibit PMN respiratory burst to prevent neutrophil extracellular traps (NETs) formation[47]; placental MSCs (PMSCs), on the other hand, enhance PMN migration via IL-8 secretion[45] and multiple anti-bacterial functions of PMNs through IL-1β secretion.[48] Such accumulation and broadening of evidence for MSC interactions with numerous leukocyte populations is extremely relevant for better tailoring of MSCT—that is, determine which tissue-specific sources or cell-derived products to use—for more effective targeting of specific diseases and/or patient subpopulations.

3 | CURRENT CLINICAL TRIALS OF MSCT FOR IMMUNE-RELATED DISEASES: OVERVIEW

As of March 2021, there were approximately 1000 clinical trials using MSCT registered on the NIH Clinical Trial Database (https://ClinicalTrials.gov/), with 491 trials (47.1%) for immune−/inflammation-mediated diseases (Figure 2). The major indications for MSCT trials involving immunomodulatory function include for graft rejection (n = 93), autoimmune diseases (n = 129), and non-immune diseases with inflammatory components (n = 269). These trials are mainly in early phases, such as Phase 1 to evaluate safety (n = 136 or 27.7%), Phase 2 to evaluate efficacy (n = 97 or 19.8%), or combined Phase 1/2 (n = 203 or 41.3%) (Table 1). Only a few trials are in Phase 3 to determine effectiveness (n = 18 or 3.7%), combined Phase 2/3 studies (n = 15 or 3.1%), and only two trials are in Phase 4 to monitor long-term effects (0.4%); 20 trials did not specify phase (4.1%). The most prevalent used sources are adult BMMSCs and adipose-derived MSCs (AdMSCs) at 35.8% and 16.9%, respectively, while the fetal source of Wharton's jelly/umbilical cord (WJUC) at 24.3% is also increasingly popular (Table 1 and Figure 3A). Other sources of MSCs utilized include from fetal sources of umbilical cord blood (UCB), placenta, and amnion tissues, as well as adult sources of menstrual blood (MB), dental pulp

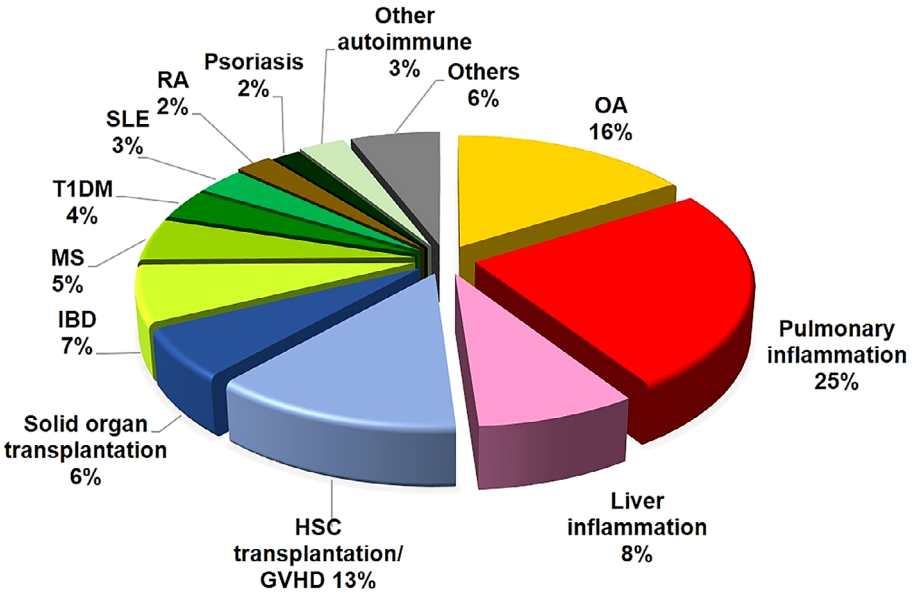

FIGURE 2 Immune and inflammatory disease indications in current clinical trials of MSC therapy. Summary of clinical trials of immune and inflammatory disease using MSC therapy as registered on the website http://ClinicalTrials.gov (accessed March 2021). OA, osteoarthritis; IBD, inflammatory bowel disease; GVHD, graft vs host disease; MS, multiple sclerosis; T1DM, type 1 diabetes mellitus; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis

TABLE 1 Current clinical trials of MSCT and derived products for immune-related diseases

			No. of clinical trial phases						
MSC source	**Total %**	**Total no.**	**N/A**	**1**	**1 and 2**	**2**	**2 and 3**	**3**	**4**
Unspecified	13.1	66	2	13	21	20	6[l]	3	1
Bone marrow	35.8	180	7	55[b]	62[c,d,e,f,g]	40[h]	7	9[i]	0
Adipose tissue	16.9	85	3	21	40[j]	16	1	4[i]	0
Umbilical cord	24.5	122	4[a]	33[b]	66[c,d,e,f,k]	17	0	1	1
Umbilical cord blood	2.8	14	1	5	4	2[h]	0	2	0
Placenta	1.0	5	0	1	2[g]	2	0	0	0
Amnion	0.4	2	1[a]	1	0	0	0	0	0
Menstrual blood	0.4	2	0	0	2	0	0	0	0
Dental pulp	0.6	3	0	2	1	0	0	0	0
Olfactory mucosa	0.4	2	0	0	2	0	0	0	0
Gingiva	0.2	1	1	0	0	0	0	0	0
Skin	0.2	1	0	0	1	0	0	0	0
ESC-MSC	0.4	2	0	1	0	0	0	0	0
iPSC-MSC[A]	0.4	2	0	1	1	0	0	0	0
MSC-derived products[B]	3.2	16	2	3	7[j,k]	2	2[l]	0	0
Total no. of clinical trial phases		491	20	136	203	97	15	18	2
Total % of clinical trial phases			4.1	27.7	41.3	19.8	3.1	3.7	0.4

Notes: [a]Trial using two sources of MSCs: WJUC and amnion; [b,c,d,e,f]Trials using two sources of MSCs: BM and WJUC; [g]Trial using two sources of MSCs: BM and placenta; [i]Trial using two sources of MSCs: BM and adipose; [h]Trial using two sources of MSCs: BM and cord blood; [j,k,l]Trials using both the MSC and its derived products. [A]Reprogrammed from peripheral blood mononuclear cells. [B]Exosomes or trophic factors collected from conditioned medium.

(DP), olfactory mucosa (OM), gingiva, and skin. For the first time, there are trials using ESC-derived MSCs (ESC-MSCs; n = 2) and iPSC-derived MSCs (iPSC-MSCs; n = 2) as well as MSC-derived products including extracted exosomes or conditioned medium (n = 16). A very clear emerging trend is the use of allogeneic over autologous MSCs in 61.6% vs 27.8%, respectively, while 10.6% of trials did not specify donor source (Figure 3B). In this review, we will focus on immune-related disease entities with a high number of ongoing clinical trials.

4 | CURRENT CLINICAL TRIALS OF MSCT FOR IMMUNE-RELATED DISEASES: SPECIFIC INDICATIONS

4.1 | Graft-vs-host disease and transplant graft rejection

The first clinical report of MSCT for immune-related diseases was in 2004 for steroid-resistant severe acute graft-vs-host disease (GVHD) in a pediatric patient post-allogenic hematopoietic stem cell transplantation (HSCT) for leukemia.[49] This successful case report rapidly led to two large-scale trials for GVHD[50] and also rapidly generated interest for use of MSCs in solid organ transplant rejection.[51,52] A number of preclinical reports support the use of MSCs for improvement of HSCT engraftment and/or GVHD, with mechanisms including suppression of effector T cells and improvement of survival in murine in vivo GVHD models through MSC-expressed IDO and PD-L1 in response to inflammatory cytokines such as IFN-γ, TNF-α, and IL-1β, all inflammatory cytokines which are elevated in GVHD patients.[53,54] MSC modulation of CD4 T cells from effector to regulatory phenotypes was also seen in an early report of solid organ transplant using a murine heart semi-allograft model,[55] with rapid accumulation of other studies on MSCs prolonging survival and/or preventing rejection of other organ/tissue types including skin,[56] pancreatic islet cells,[57] liver,[58] kidney,[59] and cornea.[60-62] A common finding in these studies is the ability of MSCs to promote IL-10-producing immune cells, surprisingly in both adaptive as well as innate leukocytes.[55,57] These early clinical and preclinical successes have made graft rejection a leading indication for use of MSCT.

Currently, there are 63 registered trials of MSCT for HSCT engraftment/GVHD, and 30 trials for prevention or treatment for solid organ transplant rejection (Table S1). The majority of these trials are Phase 1 (n = 22), Phase 2 (n = 23) or combined Phase 1/2 (n = 32), with only a small portion in Phase 3 (n = 6) and combined Phase 2/3 (n = 6); four trials did not specify phase. BM is the major source of MSCs in the trials for GVHD and graft rejection (n = 43), while a few trials utilize MSCs from adipose tissue (n = 8), WJUC (n = 7), UCB (n = 3) with one trial in comparison with BMMSCs; remarkably, there is a very recent trial using iPSC-MSCs (n = 1). However, 28 trials did not specify the source of MSCs, and two used MSC-derived products with one using exosomes from WJUCMSCs and one using conditioned medium (CM) from unspecified MSCs.

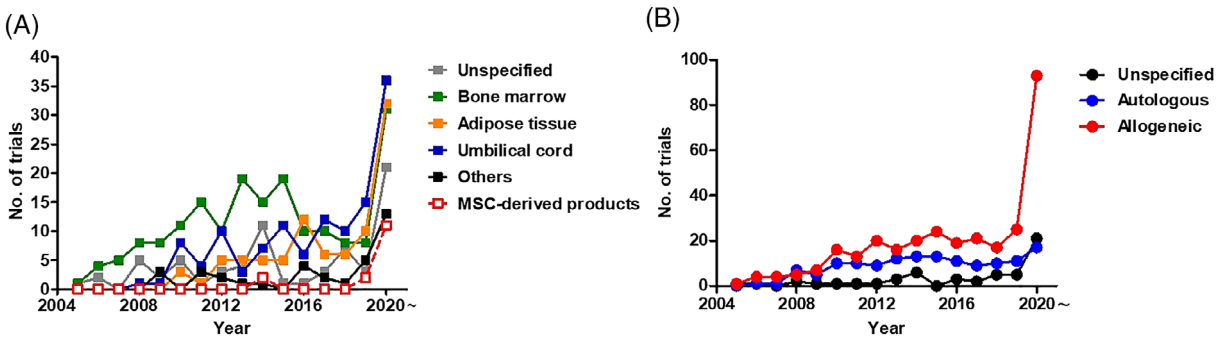

FIGURE 3 Sources of human MSCs used in clinical trials of immune/inflammatory diseases. A, Number of trials using different tissue sources of human MSCs as well as MSC-derived products, including exosomes and conditioned medium. B, Number of trials using autologous or allogenic source of human MSCs or MSC-derived products. Data accessed on March 2021 from the NIH Clinical Trial website (https://ClinicalTrials.gov/)

Interestingly, the majority of trials use allogeneic rather than autologous MSCs (57 vs 16 trials, respectively), while one trial used both types and 19 trials were undefined.

Because graft rejection was the first clinical application of MSCT, this field has the most published studies of clinical data so far, with nine reports on GVHD and 11 reports on solid organ transplantation. Several adult and pediatric trials—including two Phase 3 trials—for steroid-refractory acute or chronic GVHD using intravenous infusion of allogenic BMMSCs at doses of $1\sim2 \times 10^6$/kg showed significant therapeutic efficacy and safety[63-68]; moreover, co-transplantation of BMMSCs at the time of HSCT was found to prevent GVHD progression and/or occurrence.[69,70] One of the most exciting results is a Phase 1 trial published this year using allogeneic iPSC-MSCs for steroid-resistant acute GVHD, in which safety and some efficacy was seen.[71] Interestingly, for solid organ rejection, all seven published reports used autologous BMMSCs for renal transplantation,[72-77] and pancreatic islet cell transplantation.[78] Immunosuppressive drugs were used in all these studies except in the islet cell transplantation study and all demonstrated safety, with some efficacy seen in these studies. Allogeneic BMMSCs or WJUCMSC were used in two studies of renal transplantation, and no toxicity was seen.[79,80] When considering the efficacy of allogenic MSCs, WJUCMSCs was reported to successfully prevent both delayed graft function and acute rejection in renal transplantation,[81] whereas BMMSCs were not found to induce immunosuppression in a report on liver transplantation.[82] These published results overall demonstrate that for graft rejection, MSCT is safe and may be efficacious, especially for pediatrics cases of GVHD where allogeneic BMMSC therapy may be particularly beneficial.

4.2 | Autoimmune diseases

Autoimmune diseases are disorders in which the body's immune system attacks its own cells and organs, and autoreactive T lymphocytes—particularly CD4/helper T cells—are now known to be the critical leukocytes causing these disorders. A key finding in most autoimmune diseases is an imbalance between effector T cell subpopulations of Th1/Th17, vs immunomodulatory IL-10-producing Treg, which then lead to inflammation and injury of targeted tissues. Since MSC immunomodulation has been best demonstrated toward CD4 cells, it is no surprise that clinical trials of MSCT for autoimmune diseases collectively are the most numerous. Currently, more than 25% MSCT immune-related trials are for autoimmune diseases overall, and these 129 trials includes 34 trials for inflammatory bowel disease (IBD), 25 trials for multiple sclerosis (MS), 18 trials for type 1 diabetes mellitus (T1DM), 16 trials for systemic lupus erythematosus (SLE), 12 trials for rheumatoid arthritis (RA), 9 trials for psoriasis, and 15 trials for other autoimmune diseases (Table S2). The overwhelming majority of these trials are in early phases, with 29 in Phase 1, 15 in Phase 2, and 73 in combined Phase1/2; there are seven ongoing trials evaluating efficacy, with three trials in combined Phase 2/3, three trials in Phase 3, and one trial in Phase 4; five trials did not specify phase. Interestingly, all three Phase 3 trials are for IBD—all specifically for Crohn's disease (CD)—and use allogenic sources of BMMSCs (n = 2) or AdMSCs (n = 1). The majority of trials use either BMMSCs (n = 43) or WJUC (n = 39) with two trials using both types of MSCs together, with the next most common source being AdMSCs (n = 21); 15 trials did not unspecified MSC type. There are a few trials using UCBMSCs (n = 4), amniotic MSCs (n = 1), MBMSCs (n = 1), OMMSCs (n = 1), with one trial using BMMSC-derived neurotrophic factors (BMMSC-NFs) as well as one using UCBMSC-derived exosomes. Overwhelmingly, allogenic MSCs are utilized (n = 84) over autologous MSCs (n = 40), with three trials being undefined. Encouragingly, there are two trials comparing different sources of MSCs (autologous BMMSCs vs allogenic WJUCMSCs).

Currently, there are 26 published papers delineating the results of 29 MSCT trials for various autoimmune diseases. The most encouraging results were for CD/IBD, in which peri-fistula injections of either autologous or allogenic BMMSCs or allogenic AdMSCs promoted healing of perianal fistulas[83-86]; intravenous injection of allogenic WJUCMSCs to CD and ulcerative colitis (UC) patients also reduced mucosal inflammation.[87,88] The six published reports using autologous BMMSCs administered intravenously or intrathecally for MS demonstrated safety and some non-significant reduction of inflammatory parameters[89-94]; two other reports utilized allogeneic WJUCMSCs, with one study still ongoing[95] and one seeing benefit in several clinical

parameters.[96] For RA, both autologous BMMSCs and allogenic AdMSCs were well tolerated and trended toward efficacy.[97,98] Allogeneic BMMSCs and WJUCMSCs also appear to be safe and feasible for patients with aplastic anemia,[99] Sjögren syndrome,[100] and systemic sclerosis.[101,102] For T1DM, however, while autologous BMMSCs and allogenic WJUCMSCs demonstrated safety and potential therapeutic effect on preserving β-cell function,[103,104] allogenic AdMSCs resulted in unanticipated mild transient adverse events in T1DM patients without immunosuppression.[105] Similarly, in SLE/lupus nephritis, while allogenic BMMSCs were well-tolerated,[106] results with WJUCMSCs were discrepant with one trial showing no efficacy[107] and two trials demonstrate satisfactory clinical response via MSC-mediated IDO expression in most patients, albeit with disease relapse after 6 months in a few patients.[108,109] While most of these published clinical reports are early Phase studies focusing on safety, collectively these reports seem to imply that MSCT may be more effective for some autoimmune diseases—IBD and MS—than others. Both IBD and MS are considered to be predominantly mediated by Th17,[110111] whereas other commonly MSCT-targeted autoimmune diseases are more Th1-predominant, such as T1DM, or prominently involve non-CD4 populations, such as SLE and RA. Close attention should be paid to trial results for psoriasis, also a predominately Th17 disease, which have been numerous recently. Another variable to follow closely is whether different sources of MSCs would be particularly suited to specific diseases, since preclinical results are starting to indicate tissue-specific differences in MSC immunomodulatory mechanisms.[30,48]

4.3 | Osteoarthritis

Due to rapidly aging populations globally, osteoarthritis (OA) has become one of the most common diseases worldwide. While the pathogenesis is degradation of joint cartilage due to wear and tear, this degenerative process elicits inflammation involving macrophage-mediated activation of innate and adaptive immune responses which lead to further destruction of joint cartilage, a tissue which does not regenerate.[112] As the stem cells for chondrocytes, MSCs have long been favored for treatment of OA, and the additional benefit of immunomodulation appears to synergistically further improve outcome.[113,114] Indeed, in addition to MSC chondrogenesis, much preclinical evidence exist on the immunomodulatory efficacy of MSCT for OA, including modulation of activated M1 to alternative M2 macrophage[115,116] and priming by OA-related inflammation including IL-1β—an inflammatory cytokine critical in many joint pathologies—to further enhance MSC immunomodulation.[117,118]

Nearly 18% of all MSCT clinical trials are for OA/non-rheumatoid degenerative arthritis, and of these 79 trials, most are in early phases with 22 at Phase 1, 15 at Phase 2, and 30 at combined Phase1/2. There are six Phase 3 trials, two are combined Phase 2/3, and four are undefined (Table S3). Most of these trials use AdMSCs (n = 28), BMMSCs (n = 24) and WJUCMSCs (n = 13), with a few trials using MSCs from other tissues, including placenta (n = 1), UCB (n = 4), and DP (n = 1); three trials did not specify source. Interestingly, there are three trials which evaluated two types of MSCs simultaneously, with two trials testing BMMSCs against AdMSCs or PMSCs, and another trial evaluating WJUCMSCs to amniotic MSCs. There are two trials using MSC-derived products, with one using WJUCMSC-conditioned medium and the other using AdMSC-secretome. Surprisingly unlike for other immune diseases, autologous MSCs are most commonly used for OA (n = 43) compared with allogenic MSCs (n = 29); one trial used both autologous and allogeneic sources and six trials were unspecified. Currently, there are 15 published results of MSCT for OA, with five reports each on autologous BMMSCs[119-123] and autologous AdMSCs.[124-128] The other five reports all used allogeneic sources, including BMMSCs,[129-131] AdMSCs,[132] or WJUCMSCs.[133] All these studies demonstrated safety with intra-articular MSC injection, as well as varying degrees of improvement in symptoms and disease progression. Such consistent findings highlight MSCT as a promising treatment for OA with its burden on quality of life.

4.4 | Pulmonary inflammation and COVID-19

The high entrapment of cells within the lungs after intravenous injection—the most common method to deliver cell therapy—has long been known, and can be taken advantage of in MSCT for pulmonary diseases.[134] As an organ open to the environment, a number of infectious and non-infectious/allergic immune pathologies affect the lungs, some with lethal consequences including the post-inflammatory syndrome associated with COVID-19.[11,135] Preclinical data demonstrate that in non-infectious pulmonary diseases, MSCs can inhibit Th2 responses in asthma, as well as repair alveolar epithelial damage in obstructive diseases such as chronic obstructive pulmonary diseases (COPDs) and restrictive diseases such as idiopathic pulmonary fibrosis (IPF) through secreted factors, exosomes, and even mitochondrial transfer. In infectious pulmonary diseases including pneumonia and acute respiratory distress syndrome (ARDS), preclinical data consistently demonstrate MSCT to be most useful in suppressing overexuberate host immune responses. Such reports based on bacterial and influenza pneumonia/ARDS animal models have led to an overwhelming number of MSCT trials for COVID-19, despite the lack of preclinical evidence with this novel virus.

The numbers of MSCT clinical trials for pulmonary immune-related diseases have skyrocketed in 2020 due to the COVID-19 global pandemic, which now stands at 121 registered trials. Over half of the trials are for COVID-19 (n = 74), and a further 14 trials for pneumonia/ARDS, an inflammatory complication of severe infectious pneumonia including COVID-19. There are also two trials for asthma, 11 trials for COPD, five trials for IPF, and 15 trials for other inflammatory respiratory diseases including cystic fibrosis and radiation pulmonary injury (Table S4). The trials are predominately in early phase, with 48 in Phase 1, 28 in Phase 2, and 37 in combined Phase 1/2 trials; there is one Phase 3 trial, and three combined Phase 2/3 trials, with four trials in undefined phase. Remarkably, a whopping 92 trials utilize allogeneic MSCs—mainly BM- and WJUCMSCs—with only 12 trials using autologous sources and 17 trials undefined. Overall, BMMSCs

(n = 39), WJUCMSCs (n = 33), and AdMSCs (n = 17) are the most popular sources, with a few trials using other sources including PMSCs (n = 3), UCBMSCs (n = 1), DPMSCs (n = 2), OMMSCs (n = 1), and even ESC-MSCs (n = 1) as well as iPSC-MSCs (n = 1); 13 trials did not specify source. MSC-derived products are also popular for treatment of pulmonary diseases, with eight trials using cell-free materials including three trials using AdMSC-exosomes, one using WJUCMSC-NFs, one using BMMSC-exosomes, and three trials using extracellular vesicles (EVs) from unspecified source. Moreover, there were two trials combining MSCs and their derived products with one using WJUCMSCs and CM, and another using an undefined source of MSCs and EVs. The rapid decompensation of many pulmonary infectious diseases including COVID-19 may be the reason for prevalent use of allogeneic MSCs and cell-free products, both of which can be immediately available as off-the-shelf products.

To date, there are 12 published results demonstrating the feasibility of MSCT in pulmonary immune-related diseases. There are two Phase 1 reports[136,137] and two Phase 2 reports—the Acute Physiology and Chronic Health Evaluation III (APACHE III) trial[138] and the ARDS cue to COVID-19 (COVID-AT) trial[139]—as well as one report combining results from one Phase 1 and one Phase 2 trials[140] demonstrating safety of intravenous infusion of allogenic BMMSCs or AdMSCs for intensive care unit (ICU) patients with moderate to severe ARDS. For -COPD-related lung injury, both intravenous BMMSCs (autologous or allogeneic) and autologous AdMSCs were found to be safe, but therapeutic effects on pulmonary function were found to be variable.[141-143] Infusion of allogenic BMMSCs also well tolerated in patients with IPF or bronchiolitis obliterans syndrome (BOS) after allo-HSC transplantation,[144,145] with improvement in one trial for 3-year survival likely due to a significant increase of IL-$10^{+}CD5^{+}$ B cells in patients receiving MSCT.[145] For COVID-19, there are already two published reports on the protocol for MSCT in severely ill patients using allogenic WJUC- or DPMSCs[146,147]; additionally, one clinical case series of seven patients—not registered in the NIH clinical trial database—reported safety and efficacy with infusion of (likely) allogeneic BMMSCs.[148] Clinical results of MSCT for lung diseases—especially COVID-19—are highly anticipated because of the invaluable information these numerous trials will provide on the efficacy of not only MSCT but also MSC-related products.

4.5 | Liver cirrhosis

Liver fibrosis or cirrhosis is the end-stage manifestation of many hepatic diseases, ranging from infectious insults due to hepatitis viruses B and C, to non-infectious conditions such as alcohol abuse and non-alcoholic fatty liver disease; it is also a risk factor for hepatocellular carcinoma formation.[149] Compared with other organ systems, mechanisms involved in MSC immunomodulation for liver diseases including cirrhosis are relatively less known (Figure 4). One of the earliest reports in 2004 demonstrated that infusion of murine BMMSCs can reduce chemically-induced liver fibrosis.[150] Since then, a number of preclinical in vivo studies have demonstrated that expression of PGE_2, IDO, and TSG-6 by BMMSCs can alter the hepatic milieu from being inflammatory to tolerogenic.[151-155] EVs from human embryonic stem cell (ESC)-derived MSCs were found to

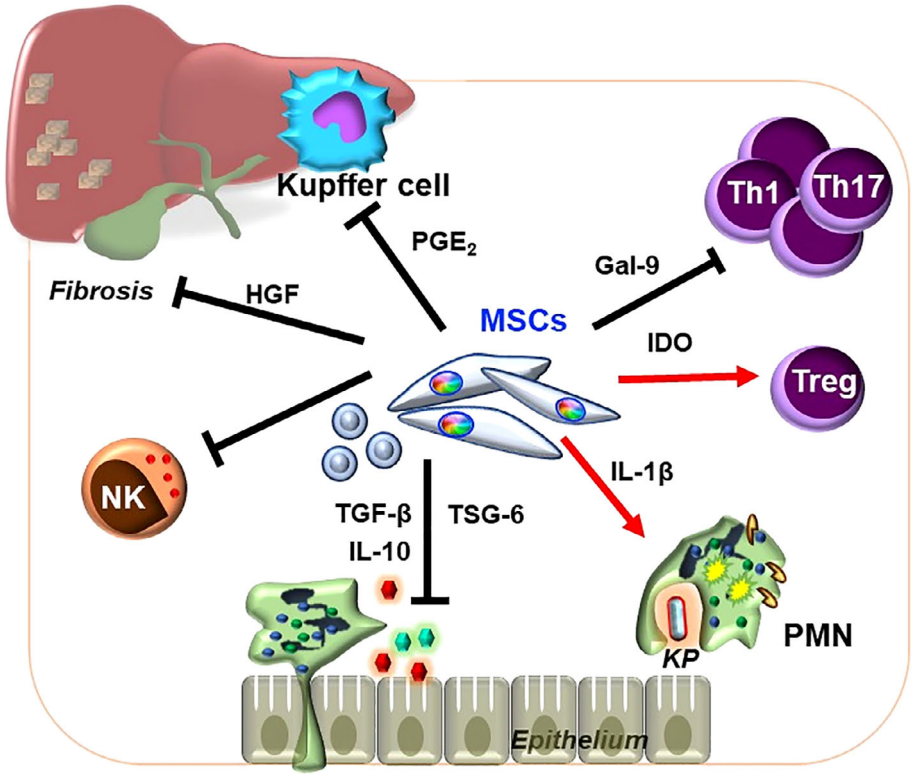

FIGURE 4 Mechanisms involved in MSCT for hepatitis or liver cirrhosis as evidenced in preclinical in vivo studies. MSC modulation of T cells and liver-resident MΦs/Kupffer cells to tolerogenic phenotypes and prevention of inflammatory cell recruitment in liver failure, as well as enhancement of anti-bacterial functions of PMNs during hypervirulent *Klebsiella pneumoniae* (*KP*) infection

contain anti-inflammatory cytokines IL-10 or TGF-β which ameliorated cirrhosis.[156] We also recently demonstrated that PMSC treatment in a mouse model of hypervirulent *Klebsiella*-induced severe intra-abdominal infection can enhance neutrophil bactericidality to reduce liver injury and increase survival.[48] In a mouse model of autoimmune cholangitis, liver inflammation was reduced through WJUCMSC-secreted Gal-9.[157] These increasing numbers of preclinical reports support that MSC immunomodulation may be efficacious toward hepatitis and cirrhosis.

Currently, there are 40 registered trials of MSCT for liver failure involving viral hepatitis or cirrhosis, with trials predominantly in early phase: six trials in Phase 1, 12 in Phase 2, and 18 in combined Phase1/2 (Table S5). Only one trial each are in Phase 3 and Phase 4; two trials did not define phase. BM (n = 16) and WJUC (n = 13) are the major sources of MSCs used in these trials, with two other trials using both sources combined. For other sources, there are two trials using AdMSCs, and one trial each using UCBMSCs, MBMSCs, and skin-derived MSCs (n = 1), as well as four undetermined sources. Again, the majority of trials use allogeneic (n = 21) over autologous sources (n = 15); one trial used both types and three trials were undefined. To date, there are only two published results, with one trial demonstrating therapeutic efficacy of autologous BMMSCs in alcoholic cirrhosis,[158] while another trial using allogenic WJUCMSCs showed limited improvement on short-term outcome of HBV-related liver failure patients.[159] Further accumulation of clinical data is urgently needed to assess whether MSCT is efficacious for inflammation-mediated liver failure and/or cirrhosis.

5 | NEW DEVELOPMENTS: USE OF MSC-DERIVED PRODUCTS AND HPSC-MSCS FOR IMMUNE-RELATED DISEASES

While the minimal reports of adverse events so far in the large number of MSC clinical trials are reassuring, efficacy has been as easy to achieve as was expected. This has increasingly led to the idea that MSC immunomodulation may be represent short-term immune evasion rather than long-term immune privilege, and that the MSC itself likely rapidly undergo apoptosis after administration.[160-162] These reports along with increasing evidence of MSC-derived products harboring immunomodulatory function, render cell-free options particularly attractive for clinical use. It is well known that paracrine factors are disproportionately responsible for MSC immunomodulatory effects,[7,8] thus it is perhaps not surprising to find MSC-derived, cell-free products to have significant efficacy for immune and inflammatory diseases. Preclinical animal data are promising, demonstrating human MSC-EVs to be efficacious for GVHD and numerous autoimmune diseases including EAE, T1DM, and RA.[163] Moreover, in addition to CD4 T cells, MSC-derived products have been shown to modulate numerous other types of leukocytes including B cells,[164] NK cells,[165] macrophages,[166] and DCs.[167] To date, there are 16 trials using MSC-derived products including CM, EVs, or exosomes: three trials are in Phase 1, two in Phase 2, seven are combined Phase 1/2, two are combined Phase 2/3 trials, and two did not specify phase (Table 2). Interestingly, most of the trials (n = 10) are for pulmonary diseases,[11] with mode of delivery ranging from intravenous injection for severely affected COVID-19 patients, to aerosol inhalation of AdMSC-derived exosomes in healthy volunteers and bacterial ARDS patients, and intranasal injection of WJMSC-derived trophic factors in asthma patients. Other disease indications in which MSC-derived products are applied include two trials using WJUCMSC-exosomes or MSC-CM (unspecified source) for transplant rejection, two trials using WJUCMSC-exosomes or BMMSC-derived neurotrophic factors for the autoimmune diseases of T1DM and MS, and two trials using AdMSC-secretome or WJUCMSC-CM for OA. The rising popularity of MSC-free derivatives is also evident in 16 trials for non-immune diseases which include neural degeneration, wound repair, and ophthalmological conditions (Table S6). It can be anticipated that clinical trials using MSC-derived products—readily available as off-the-shelf products—will continue to increase.

The ability to isolate MSCs from a myriad of organs/tissues does not solve the problem that all tissue-derived MSCs undergo senescence, which not only decreases proliferative capacity but differentiation capacity as well.[168,169] While there is no data currently demonstrating a loss in MSC immunomodulatory capacity with senescence, the decreased proliferative capacity associated with senescence significantly reduces *ex vivo* cell volumes to the extent that clinical use may no longer be feasible. Thus, there has always been interest in efficient derivation of MSCs from pluripotent stem cells[170]—including ESCs[171-174] and more recently, induced pluripotent stem cells (iPSCs)[175]—which express telomerase and provide essentially continuous cell sources. The concerns with using ESCs and iPSCs have always been the fear of teratoma formation due to undifferentiated cells, along with the additional fear of cancer formation in iPSCs with its higher genetic and epigenetic instability.[176] These concerns can be precluded with stringent QA/QC protocols to exclude undifferentiated and genetically unstable cells.[177] In addition, the functional variability with primary-isolated human samples and cell products is avoided since MSCs can be generated from a particular ESC or iPSC line essentially indefinitely to continually provide functionally stable lots of cells and cell products.[178] While a few reports relying on only one or two hPSC lines did not find immunomodulatory functions,[179,180] most studies found both ESC-MSCs and iPSC-MSCs to be similar to BMMSCs in terms of low immunogenicity and strong immunomodulation toward T cells and NK cells[175,181-183]; these findings likely explain the capacity of MSCs to prevent graft rejection since both lymphocyte populations are critically involved in inducing alloreactivity.[184,185] Very recently, preclinical data on cell-free products derived from ESC-/iPSC-MSCs have emerged as well, with therapeutic immune outcome seen.[156,186] Currently, there are two trials using ESC-MSCs for COVID-19 (combined Phase1/2) and interstitial cystitis (Phase 1) registered in 2020; and two trials using iPSC-MSCs (CYP-001) from the same sponsor for GVHD (Phase 1) registered in 2016, and for COVID-19/ARDS (combined Phase1/2) registered in 2020. Results from the GVHD trial have just been published, in which safety was found with some efficacy seen in this exciting

TABLE 2 Clinical trials for immune-related diseases using MSC-derived products

Condition	NCT number	Title	Status	Delivery	Auto/allo?	Source MSCs	Age	Phase	First posted
Asthma	NCT02192736	Safety and Feasibility Study of Intranasal Mesenchymal Trophic Factor (MTF) for Treatment of Asthma	Active, not recruiting	Intranasal	Allo	WJUCMSC-TFs	21 to 60 years	Phase 1|Phase 2	July 17, 2014
ARDS	NCT04544215	A Clinical Study of Mesenchymal Progenitor Cell Exosomes Nebulizer for the Treatment of Pulmonary Infection	Recruiting	Aerosol Inhalation	Allo	AdMSC-Exo	18 to 75 years	Phase 1|Phase 2	September 10, 2020
ARDS	NCT04602104	A Clinical Study of Mesenchymal Stem Cell Exosomes Nebulizer for the Treatment of ARDS	Not yet recruiting	Aerosol Inhalation	Allo	UNS-MSC-Exo	18 to 70 years	Phase 1|Phase 2	October 26, 2020
COVID-19	NCT04276987	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	Completed	Aerosol Inhalation	Allo	AdMSC-Exo	18 to 75 years	Phase 1	February 19, 2020
COVID-19	NCT04366063	Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome	Recruiting	IV	UNS	UNS-MSCs/MSC-EVs	18 to 65 years	Phase 2|Phase 3	April 28, 2020
COVID-19	NCT04398303	ACT-20 in Patients With Severe COVID-19 Pneumonia	Not yet recruiting	IV	Allo	WJUCMSCs/MSC-CM	18 to 85 years	Phase 1|Phase 2	May 21, 2020
COVID-19	NCT04657458	Expanded Access Protocol on Bone Marrow Mesenchymal Stem Cell Derived Extracellular Vesicle Infusion Treatment for Patients With COVID-19 Associated ARDS	Available	IV	UNS	BMMSC-Evs	18 years and older	Not Applicable	December 8, 2020
COVID-19	NCT04753476	Treatment of Severe COVID-19 Patients Using Secretome of Hypoxia-Mesenchymal Stem Cells in Indonesia	Recruiting	IM	UNS	UNS-MSC-secretome	Child, Adult, Older Adult	Phase 2	February 15, 2021
COVID-19	NCT04798716	The Use of Exosomes for the Treatment of Acute Respiratory Distress Syndrome or Novel Coronavirus Pneumonia Caused by COVID-19	Not yet recruiting	IV	UNS	UNS-MSC-Exo	18 years and older	Phase 1|Phase 2	March 15, 2021
Lung injury test in HD	NCT04313647	A Tolerance Clinical Study on Aerosol Inhalation of Mesenchymal Stem Cells Exosomes In Healthy Volunteers	Recruiting	Aerosol Inhalation	Allo	AdMSC-Exo	18 to 45 years	Phase 1	March 18, 2020
OA	NCT04314661	Comparative Effectiveness of Arthroscopy and Non-Arthroscopy Using Mesenchymal Stem Cell Therapy (MSCs) and Conditioned Medium for Osteoartrithis	Recruiting	Intraarticular	Allo	WJUCMSCs/MSC-CM	55 to 70 years	Phase 1|Phase 2	March 19, 2020

TABLE 2 (Continued)

Condition	NCT number	Title	Status	Delivery	Auto/allo?	Source MSCs	Age	Phase	First posted
OA	NCT04223622	Effects of ASC Secretome on Human Osteochondral Explants	Not yet recruiting	Unspecified	UNS	AdMSC-secretome	18 years and older	Not Applicable	January 10, 2020
GVHD with dry eye	NCT04213248	Effect of UMSCs Derived Exosomes on Dry Eye in Patients With cGVHD	Recruiting	On eye	Allo	WJUCMSC-Exo	18 to 70 years	Phase 1|Phase 2	December 30, 2019
T1DM	NCT02138331	Effect of Microvesicles and Exosomes Therapy on β-cell Mass in Type I Diabetes Mellitus (T1DM)	Unknown status	IV	Allo	UCBMSC-Exo	18 to 60 years	Phase 2|Phase 3	May 14, 2014
MS	NCT03799718	Safety and Efficacy of Repeated Administration of NurOwn (MSC-NTF Cells) in Participants With Progressive MS	Recruiting	Intrathecal	Auto	BMMSC-NFs	18 to 65 years	Phase 2	January 10, 2019
Skin transplant	NCT04234750	Mesenchymal Stem Cell-derived Pleiotropic Factor in the Treatment of Donor Sites	Recruiting	On skin	UNS	UNS-MSC-CM	6 to 60 years	Phase 1	January 21, 2020

Abbreviations: Ad, adipose; allo, allogenic; Auto, autologous; IV, intravenous; TF, trophic factor; UCB, umbilical cord blood; UNS, unspecified; WJUC, Wharton's jelly/umbilical cord.

milestone.[71] Based on increasing preclinical data and these four sentinel trials, it is anticipated that more clinical trials using hPSC-derived MSCs will be conducted.

6 | PERSPECTIVES ON CHALLENGES IN MSCT

Although there are over 1000 trials using various types of MSCs or MSC-free derivatives being conducted in more than 40 countries, only nine MSC-based products have been approved worldwide for either regenerative or immune-related diseases.[187] Encouragingly, these approved MSC-based products overwhelmingly except for one product are for immune-related indications, and include allogenic AdMSCs approved by the European Medicines Agency of the European Union to treat complex perianal fistulas in adult CD patients; allogenic BMMSCs approved by Health Canada in Canada, Medsafe in New Zealand, and the Therapeutic Goods Administration in Australia to treat acute GVHD in pediatric patients 2 to 17 years-old who failed previous therapies for GVHD; and allogenic BMMSCs approved by the Pharmaceuticals and Medical Devices Agency in Japan to treat acute GVHD after allo-HSC transplantation. In Korea, the Ministry of Food and Drug Safety have authorized three MSC products, including autologous BMMSCs for acute myocardial infarction, allogenic WJUCMSCs for OA, and autologous AdMSCs for CD.

While clinical effectiveness is ultimately the criteria for approval of therapeutic products, the low numbers of approved MSC products also reflect large national/regional differences in regulation for cell-based products,[188] as well as difficulties in transitioning from preclinical to clinical platforms.[189] MSC products in particular suffers from a lack of agreement on robust and relevant characterization criteria for clinical reliability and functionality; the current Minimal Criteria for MSCs date back nearly two decades and was not established for clinical use nor take into account immunomodulatory properties which were largely discovered after these criteria were agreed upon. Moreover, "gold standard" double-blind randomized clinical trial—including testing for critical parameters such as dose, delivery route, and timing—are clearly more difficult to conduct with complex and live cell-based products than pharmaceutical products.[178] Continually progress to overcome these hurdles is occurring which should allow for clinical effectiveness to be more evident in the near future.[187]

7 | CONCLUSION

MSCT for immune and inflammatory diseases continue to rise in popularity, with a clear trend seen on increasing use of allogeneic sources—especially WJUC and AdMSCs—likely for biological as well as commercial reasons. Approximately 16% of immune-related trials have now reported some results, most being early phase trials in which safety have largely been demonstrated. While reports of therapeutic endpoints are scarce and still emerging, efficacy have been most consistently reported for specific indications: pediatric cases of

GVHD, predominately Th17-mediated autoimmune diseases such as IBD and MS, and OA in which both the regenerative and immunomodulatory capacity of MSCs can be useful. New developments in use of cell-free products and iPSC-MSCs, as well as more preclinical data on tissue-specific differences in MSC sources are all likely to further improve MSCT outcomes in the very near future.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

L.T.W.: conception, manuscript writing, final approval, funding, data research and organization; M.L.Y. and B.L.Y.: conception, manuscript writing, final approval, funding; K.J.L. and H.K.S.: manuscript editing.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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