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ISCT Committee Paper

International Society for Cell & Gene Therapy Stem Cell Engineering Committee: Cellular therapies for the treatment of graft-versus-host-disease after hematopoietic stem cell transplant

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ABSTRACT

Background aims: Allogeneic hematopoietic stem cell transplant is a curative approach for many malignant and non-malignant hematologic conditions. Despite advances in its prevention and treatment, the morbidity and mortality related to graft-versus-host disease (GVHD) remains. The mechanisms by which currently used pharmacologic agents impair the activation and proliferation of potentially alloreactive T cells reveal pathways essential for the detrimental activities of these cell populations. Importantly, these same pathways can be important in mediating the graft-versus-leukemia effect in recipients transplanted for malignant disease. This knowledge informs potential roles for cellular therapies such as mesenchymal stromal cells and regulatory T cells in preventing or treating GVHD. This article reviews the current state of adoptive cellular therapies focused on GVHD treatment.
Methods: We conducted a search for scientific literature in PubMed® and ongoing clinical trials in clinicaltrial.gov with the keywords "Graft-versus-Host Disease (GVHD)," "Cellular Therapies," "Regulatory T cells (Tregs)," "Mesenchymal Stromal (Stem) Cells (MSCs)," "Natural Killer (NK) Cells," "Myeloid-derived suppressor cells (MDSCs)," and "Regulatory B-Cells (B-regs)." All the published and available clinical studies were included.
Results: Although most of the existing clinical data focus on cellular therapies for GVHD prevention, there are observational and interventional clinical studies that explore the potential for cellular therapies to be safe modalities for GVHD treatment while maintaining the graft-versus-leukemia effect in the context of malignant diseases. However, there are multiple challenges that limit the broader use of these approaches in the clinical scenario.

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Conclusions: There are many ongoing clinical trials to date with the promise to expand our actual knowledge on the role of cellular therapies for GVHD treatment in an attempt to improve GVHD-related outcomes in the near future.

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Introduction

Allogeneic hematopoietic stem cell transplant (allo-HSCT) is curative for many malignant and non-malignant hematologic conditions, including leukemias, primary immunodeficiency disorders, bone marrow failure syndromes and metabolic diseases. Inherent to the process of allo-HSCT is the risk of acute and chronic graft-versus-host disease (GVHD), which are multisystem disorders occuring when donor immune cells recognize the recipient as foreign. All allo-HSCT regimens include *in vivo* or *ex vivo* prophylaxis for GVHD, as in its absence, hyperacute GVHD is almost uniformly fatal [1].

Acute GVHD is primarily a T-cell mediated process that develops early after transplant when donor T cells transferred with the graft are activated by the inflammatory cytokine milieu that results from tissue injury associated with cytoreduction. In contrast, chronic GVHD typically occurs later after transplant with weaning of immune suppression and recovery of donor-derived immunity. It is increasingly evident that chronic GVHD involves not only donor-derived T cells but also components of both donor and recipient humoral and innate immunity [2].

Established risk factors for developing acute and chronic GVHD include human leukocyte antigen (HLA) disparity, graft source (bone marrow versus peripheral blood versus cord blood), sex disparity (female donors for male recipients), multiparity, the intensity of conditioning, donor and recipient age, CMV serostatus, GVHD prophylaxis and previous acute GVHD [3] In addition, specific HLA alleles [4] and disruptions to the microbiome [5] have been identified more recently as risk factors.

Despite advances in donor selection, conditioning regimens, the expanded use of *in vivo* and *ex vivo* T-cell depletion and biomarkers to guide therapies, transplant recipients continue to experience a high burden of GVHD-related morbidity and mortality. Overall, approximately 40% of all recipients of allo-HSCT experience moderate-to-severe acute GVHD, whereas the incidence varies considerably depending on the risk factors described previously [6]. By contrast, chronic GVHD occurs in 50–70% of allo-HSCT recipients but is less common after cord blood and T-cell–depleted transplant and most common after peripheral blood stem cell transplants [7]. The 1-year survival rate for patients who develop severe acute GVHD (grade III-IV) is approximately 40% [8], whereas chronic GVHD represents the leading cause of late transplant-related mortality [9].

Strategies for the prevention of acute GVHD include the combination of a calcineurin inhibitor (cyclosporine or tacrolimus) with methotrexate, *ex vivo* depletion of donor T cells and administration of cyclophosphamide shortly after infusion of donor cells. Additions to this list have been anti-thymocyte globulin, corticosteroids, mycophenolate mofetil (MMF), sirolimus and most recently, abatacept [10]. No approach entirely eradicates GVHD and its clinical manifestations, but the most effective method for prevention of acute and chronic GVHD is with T-lymphocyte depletion. The mechanisms by which pharmacologic agents impair expansion (proliferation) and/or function (activation) of adoptively transferred T cells have revealed the critical events that lead to the activation of alloreactive T cells and the subsequent amplification of the signals involved in T-cell proliferation. For instance, sirolimus, a mammalian target of rapamycin pathway modulator, inhibits lymphocyte activation while preserving regulatory T cells (Tregs) [2]. Similarly, it has been demonstrated that corticosteroids partially suppress GVHD via increasing absolute Tregs numbers [11]. Likewise, although the exact immune modulatory effects of extracorporeal photopheresis (ECP) as a treatment for GVHD are not fully defined, it has been shown to increase proportions of Tregs, Th22 and follicular helper T (tfh) cells leading to balanced immune reconstitution [12]. Hence, such understanding also reveals potential roles for cellular therapies to prevent or treat GVHD.

The mechanisms by which current therapies prevent and treat GVHD reveal components of the biology of alloreactivity and its control that are potentially modifiable with cellular therapies.

Targeting T-Cell Proliferation and Activation

MMF and methotrexate are anti-metabolites interfering with DNA synthesis and thus the proliferation of antigen-activated T cells. Calcineurin inhibitors decrease T-cell activation by inhibiting interleukin-2 (IL-2) transcription. By binding to cyclophilin and FK-506 binding protein, respectively, cyclosporine and tacrolimus prevent nuclear translocation of the nuclear factor of activated T cells, decreasing T-cell function. Basiliximab and daclizumab are IL-2 receptor antagonists with emerging results in steroid-refractory GVHD (SR-GVHD) [13]. Like tacrolimus, sirolimus binds to the intracellular FK-506 protein but at a different site that leads to inhibition of the mammalian target of rapamycin complex, preventing cell-cycle entry and thus T-cell proliferation. Particularly impaired is the proliferation of CD8 T cells as well as development, activation and antigen presentation by dendritic cells. Notably, compared with calcineurin inhibitors, sirolimus spares Tregs development, which is IL-2 dependent [14]. Although these pathways do not have an apparent cell-mediated target, the relative sensitivity of different populations of T cells (e.g., Tregs) to the different agents is informative.

Targeting Costimulatory Molecules

The primary role of co-stimulation is to propagate T-cell responses and induce T-cell proliferation and cytokine secretion. The most extensively studied co-stimulatory pathways are those between the B7 proteins, CD80 and CD86 and the activating CD28 and inhibitory CTLA-4 receptors. Abatacept, a soluble CTLA-4 analog, targets CD80 and CD86, blocking the interaction with CD28, thus interfering with T-cell activation while only mildly impairing CTLA4 function [10]. Other co-stimulatory molecules whose inhibition might be associated with modulation of GVHD are CD40 and the tumor necrosis factor (TNF) family molecules.

Targeting T-Cell Signal Transduction

The JAKs initiate cytokine-triggered signaling events by activating the STAT proteins. Inhibition of this pathway has an approved indication for the treatment of SR-GVHD [1].

It is possible that infusion of T cells with higher or lower sensitivity to the effects of these agents could be synergistic with the agents and could potentially provide modifiable T-cell immunity.

Targeting Specific Subsets of T Cells

Specific subsets of T cells have relatively higher or lower capacity to induce GVHD (e.g., memory versus naïve, regulatory versus conventional, TCRα/β versus TCRγ/δ, and Th1 vs Th17 T cells). As a result, a variety of both *in vitro* and *in vivo* approaches targeting specific populations of T cells are being explored. In the last several years, T-cell depletion (TCD) strategies that target specific subsets of T cells (e.g., α/β TCD) have demonstrated preservation of the protection from GVHD associated with broader depletion strategies despite infusion of γ/δ T cells. In addition, targeting of Th17 has been investigated [15]. As achieved with a number of these agents, one of the most promising approaches is the enhancement of Tregs. Naturally occurring Tregs both directly suppress autoreactive lymphocytes and control innate immune responses [16]. Sirolimus, low-dose IL-2, ECP and azacytidine have all been associated with increased proportions of Tregs in the post-transplant period.

Proteasome inhibitors, such as bortezomib, have inhibitory effects on cytokine signaling and nuclear factor-κB activation. Bortezomib, even at very low doses, can specifically deplete alloreactive T cells, promote Treg cell survival and attenuate IL-6–mediated T-cell differentiation [17].

Agents That Target Antigen-Presenting Cells (B Cells)

Altering the presentation of non-self antigens to donor T cells is an additional potential avenue to decrease alloreactivity. Rituximab, histone deacetylase inhibitors and ECP have all been shown in at least pre-clinical models to target antigen-presenting cells of both donor and host origin [18].

Although the standard-of-care first-line therapy for treatment of GVHD remains high-dose corticosteroids, the armamentarium of targeted agents continues to not only expand but to improve our understanding of the mechanisms by which alloreactivity can be controlled. Augmenting these agents, cellular therapies such as CD4 Tregs, mesenchymal stromal cells (MSCs), and natural killer (NK) cells are being evaluated as potential therapeutic approaches for SR-GVHD. This article aims to review cellular therapies being developed for the treatment of acute and chronic GVHD.

Cellular Therapies

Regulatory T cells (Tregs)

Tregs are identified by co-expression of CD4 and CD25 (IL-2 receptor) and transcription factor FoxP3 (which controls Treg development and stability) and normally represent approximately 5–10% of all circulating CD4 T cells [19]. Tregs primarily originate in the thymus, but an additional population of Tregs (iTregs) can be induced under very specific conditions *in vivo* and can also be induced and expanded *in vitro* [16]. *In vitro*–derived iTregs are functionally suppressive in animal models of not only GVHD but inflammatory bowel disease [20], autoimmune gastritis [21] and Foxp3-deficiency [22]. Although the specific mechanism of action may vary across disease settings, the

Table 1
Observational and interventional clinical studies of adoptive transfer of Tregs or infusion of IL-2 as treatment for GVHD.

Authors and publication year (reference)	Study design	Primary objectives	Number of participants (n)	Intervention	Outcomes at day 28 or as noted*	Conclusion
Trzonkowski *et al*., 2009 [27]	Clinical trial	Describe the method and response of Tregs for GVHD treatment	2 adults	*Ex vivo*–expanded Tregs	Significant alleviation of cGVHD symptoms, but only transient response for aGVHD.	Tregs exerts some suppressive effect and should be considered as an adjuvant treatment.
Koreth *et al*., 2011 [28]	Observational cohort study	Safety and clinical/immunologic response of LD IL-2	29 adults, but 23 evaluated	Daily LD IL-2 for 8 weeks to induce Tregs	CR = 0% PR = 52% SD = 48%	Daily LD IL-2 dose was safe and improved cGVHD manifestations.
Theil *et al*., 2015 [29]	Clinical trial	Stability, safety and efficacy of Tregs for cGVHD	5 adults	Allo-Tregs of the corresponding HLA-matched donors	CR = 0% PR = 40 % SD = 60 %	Tregs isolation is feasible and reproducible for clinical application.
Koreth *et al*., 2016 [30]	Phase 2 clinical trial	Clinical efficacy of LD IL-2 therapy	35 adults, but 33 evaluated	Daily IL-2 to induce Tregs	CR = 0% PR = 62% SD = 30% *Assessment at week 12.	LD IL-2 is well tolerated and provides durable clinical improvement in active cGVHD.
Whangbo *et al*., 2019 [31]	Phase 1 clinical trial	Safety and MTD of escalated IL-2	11 children, 10 adults	IL-2 dose escalation to enhance Tregs expansion.	CR = 0%. Children: PR = 82% Adults: PR= 29%	LD IL-2 is safe and effective in children with cGVHD. In adults, dose escalation did not improve clinical response.
Whangbo *et al*., 2022 [32]	Phase 1 clinical trial	Safety and MTD of Tregs-enriched cells plus 8-week LD IL-2 in patients with SR-cGVHD.	25 Adults	Tregs-enriched lymphocytes and *in vivo* LD IL-2.	CR = 0%. PR = 20% SD = 40% *Assessment at week 8	Infusion of Tregs followed by expansion with LD IL-2 is safe in patients with SR-cGVHD.
Donato *et al*., 2022 [33]	Observational Cohort Study (Retrospective Chart Review)	Long-term clinical/immunologic outcomes after stopping LD IL-2.	22	LD IL-2	73% of the patients weaned off all the immunosuppressive therapy (median follow-up: 203 weeks)	Clinical improvement with LD IL-2 was durable.

aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CR, complete response; GVHD, graft-versus-host disease; IL-2, interleukin 2; LD, low dose; MTD, maximum tolerated dose; PR, partial response; SD, stable disease; SR-GVHD, steroid-refractory graft-versus-host disease.

Table 2
Ongoing clinical trials of adoptive transfer of T-reg or infusion of IL-2 as treatment of GVHD after allo-HSCT.[a]

Study	Status	Target population/disease	Intervention	Primary outcome	Location
NCT04678401	Recruiting	18–65 y of age/GVHD	Haplo-HSCT Tregs-enriched CD34+ PBSCs	MTD	DFCI Boston, MA
NCT01937468	Not recruiting	18 y of age and older/c GVHD	Tregs-enriched T cells IL-2	MTD Safety profile	DFCI/BWH Boston, MA
NCT01903473	Recruiting	18–80 y of age/acute, chronic and SR-GVHD	Rapamycin Tregs	Safety profile	Belgium
NCT02749084	Recruiting	18 y of age and older/cGVHD	T regs DLI	OR at week 12	Bologna, Italy
NCT05095649	Recruiting	All ages/chronic GVHD	Tregs-enriched infusion	OR at week 23	Sevilla, Spain
NCT01366092	Not recruiting	18 y of age and older/cGVHD	IL-2	OR at week 6 and 12 *preliminary results	DFCI/BWH Boston, MA
NCT02340676	Not recruiting	18 y of age and older/GVHD	ECP, IL-2	OR at week 16 *preliminary results	DFCI Boston, MA

cGVHD, chronic graft-versus-host disease; BWH, Brigham and Women's Hospital; DLI, donor lymphocyte infusion; DFCI, Dana-Farber Cancer Institute; MTD, maximum tolerated dose; OR, overall response. SR-GVHD, steroid-refractory graft-versus-host disease.
[a] Retrieved from clinicaltrials.gov on October 2, 2022.

prevention of autoimmunity [23,24] makes it rational to explore them as modifiers of GVHD.

In pre-clinical studies, Tregs have been shown to promote bone marrow engraftment and decrease the incidence and severity of GVHD [25] and control GVHD while sustaining the graft versus leukemia (GVL) effect [26]. Table 1 summarizes observational and interventional clinical studies related to Tregs or low-dose IL-2 for GVHD [27–33].

Most of the clinical trials performed to date have explored GVHD prophylaxis [24]. Brunstein *et al.* [34] studied the safety and outcomes of 11 patients treated with umbilical cord blood–derived Tregs compared with 22 patients treated with the same conditioning and GVHD prophylaxis (sirolimus/MMF). The cumulative incidence of acute GVHD was lower in the experimental group versus the control group without an increased incidence of infection or relapse. Similarly, the combination of low-dose IL-2 and adoptive infusion of *in vitro*–expanded Tregs has been explored for GVHD prevention [35]. An additional phase 1 clinical trial performed in 14 recipients of HLA-identical sibling reduced-intensity peripheral blood stem cell transplantation demonstrated the safety of adoptively transferred iTregs [29]. Early experience with adoptive transfer of *ex vivo*–expanded Tregs into five adult patients with SR-GVHD demonstrated partial responses (PR) in two of them [36].

As an alternative to infusion of Tregs, low-dose infusion of IL-2 with the goal of *in vivo* expansion of Tregs was evaluated by Koreth *et al.* [28] in 29 adult patients and in a dose escalation trial in 10 adult and 11 pediatric patients by Whangbo *et al.* [31]. Investigators concluded that a daily low IL-2 dose was safe and improved the manifestations of chronic SR-GVHD in a substantial number of patients but did not mediate complete responses. In a similar fashion, patients with SR-GVHD received a single infusion of donor-derived Treg-enriched lymphocytes (Treg-DLI) supported by *in vivo* low-dose IL-2 [32]. PR were reported in five of 25 patients after 8 weeks of therapy, with an additional 10 patients having clinical improvement not meeting criteria for PR. It is yet to be demonstrated whether greater doses of Tregs can achieve complete responses in these patients.

Although promising results have been demonstrated in the setting of acute, chronic and SR-GVHD, with multiple ongoing clinical trials evaluating the safety and efficacy of adoptively transferred HSCT donor or third-party donor-derived Tregs (Table 2), various challenges need to be tackled to move forward with the development of this therapy for GVHD. First, the biology of Tregs has yet to be entirely understood. For example, recent studies have studied a different Tregs subset, CD8+ Tregs, and little is known about their function against GVHD [37]. In the same train of thought, if the biology comprehension is uncertain, logically, this affects the process of isolating and purifying these cells (incomplete understanding of cell surface markers) from third-party donors. Similarly, there are no commercial Tregs products, which could be secondary to the costly and well-known complex manufacturing processes. Therefore, current clinical trials use their manufacturing process, which brings additional heterogeneity when interpreting the outcomes. Also, different timing and doses of administration, primary outcomes, and assessment days have been evaluated in the ongoing trials, making it difficult to interpret and compare these outcomes and apply these results to clinical practice.

There is an emerging role for Tregs in the prevention and treatment of GVHD. The next hurdle is to harness this by infusion of purified populations of Tregs or alternatively enhancing the *in vivo* differentiation, proliferation and survival of these populations

Mesenchymal Stromal Cells

MSCs can be isolated from multiple tissues, but most of the experience in GVHD has relied on bone marrow (BM)-derived MSCs, defined by low levels of major histocompatibility complex class I molecules, CD105, CD73, CD90 and lack of the expression of major histocompatibility complex class II molecules, CD40, CD80, and CD86. Although the mechanism of action of MSCs likely differs across treatment settings and is incompletely understood, it is increasingly appreciated that in response to the specific inflammatory milieu, they possess immunomodulatory and immunosuppressive functions, including T-cell inactivation, inflammatory response suppression and increased secretion of immunosuppressive factors [38]. A recent preclinical study demonstrated the requirement of interferon-γ licensing for inducing MSCs. In addition, this study showed that ruxolitinib, a JAK inhibitor, blocks interferon-γ, which might inhibit the immunomodulatory effect of MSCs [39].

In the clinical setting of GVHD prevention, a phase 1 clinical trial reported the use of intra-BM injections of MSCs combined with cord blood transplantation [40]. The primary aim was to assess toxicity associated with intra-BM injection of MSCs, but investigators also assessed their role in GVHD prophylaxis. No adverse events related to intra-BM injection of MSCs were reported. Grade II-IV acute GVHD developed in 50% of the controls; however, no acute GVHD was observed in the intervention (MSCs) group. No patient in either group developed chronic GVHD consistent with the overall low incidence of chronic GVHD after cord blood transplantation. This study demonstrated the safety of the intervention, and the findings suggested that co-transplantation of MSCs may prevent GVHD [40].

The potential efficacy and safety of MSCs for the treatment of a pediatric patient with severe GVHD was reported as a single case in 2004 [41]. Since that time, there have been case series, phase 2 [42,43] and phase 1/2 [44] trials with mixed results (response rates

between 54% and 86%) and the suggestion that in pediatric patients with severe acute GVHD, they can improve survival outcomes.

Subsequent trials have reported on Remestemcel-L, a commercial preparation of human BM-derived MSCs [45]. Although these studies have not met their primary endpoints (response rate at day 28), in an unplanned subset analysis 58% of pediatric patients with refractory grades III and IV acute GVHD demonstrated complete responses. A subsequent phase 3 trial conducted in pediatric patients with SR-GVHD in the absence of additional immunosuppressive therapy demonstrated an overall response (OR) of 70.4% on day 28 compared with the historical control OR of 45% (P = 0.0003) [46]. Similar results were maintained through day 100. These results translated into overall survivals of 74.1% and 68.5% at days 100 and 180, respectively. In an expanded access study, 242 subjects were treated at 50 sites in eight countries (the USA, Canada, UK, Italy, Finland, Spain, New Zealand and Australia) with similar results with an OR of 65.1% on day 28 and survival of 66.9% at day +100 [47]. However, Remestemcel-L failed to gain approval from the Food and Drug Administration [48] for this indication.

Table 3 summarizes observational and experimental clinical studies evaluating MSCs for GVHD treatment [49–68], and Table 4 summarizes ongoing clinical trials registered on clinicaltrial.gov using MSCs for GVHD treatment. It is evident that the literature in this field is dominated by observational studies (case reports and cohort studies), early-phase clinical trials and a few phase 3 interventional trials that have reported mixed results. There are many possible reasons for such apparent heterogeneity in the efficacy (although not safety) of MSCs for the treatment of GVHD, including differences in patient populations, but, likely, differences in MSCs' product characteristics are also critical. For example, unlike Tregs, a commercial MSC product is available on the market, but current clinical trials use their own manufacturing methods, a significant variable that undoubtedly impacts the outcomes. Likewise, identified differences linked to both in vitro measures of efficacy and clinical efficacy include age and sex of the MSC donor, manufacturing approach, passage number, and cryopreservation [69]. For example, van der Wagen *et al.* [70] demonstrated that MSC donor age (hazard risk 2.006, confidence interval 1.091–3.687, P = 0.025) was an independent factor contributing to recipient survival. Specifically, a survival benefit for patients treated with MSCs derived from young (<10 years of age) versus older donors was noted. Therefore, these previously published studies have multiple confounders, making it impossible to compare their results. To resolve these differences and advance the field, a better understanding of the relative importance of donor, source, manufacturing approach, and infusion strategy is urgently needed. Similarly, ongoing clinical trials must harmonize their primary outcomes and endpoints (e.g., complete response (CR) at day 28) to be able to compare efficacy results across the studies. In addition, long-term follow-up data must be collected and analyzed to evaluate the durability of this novel therapy.

As a better understanding emerges of the mechanism of action and inflammatory milieu in which MSCs have their best activity, it is hoped that clinical trials will be able to define the patients for whom this modality is an appropriate therapy.

Other cell therapies that have been studied in humans

NK cells

NK cells are part of the innate immune system that mediates anti-tumor and antiviral responses, destroying cancer or infected cells. NK cell-mediated cytotoxicity and cytokine release can interfere with the activity of different innate immune cells such as neutrophils, giving NK cells a regulatory function capable of influencing the subsequent antigen-specific, HLA-restricted T- and B-cell responses. After HSCT, NK cells are typically the first lymphocytes to reconstitute. Greater absolute numbers of NK cells in the early post-transplant period have been associated with improved survival and a lower relapse incidence, suggesting a GVL effect [71].

The role of donor NK cells in propagating or preventing GVHD is controversial. In their review, Simonetta *et al.* [71] attempted to clarify the dual role of NK cells in GVHD by outlining the effector and regulatory functions that NK cells have. This is the most likely rationale behind the variable roles that NK cells can manifest during GVHD.

Overall, there is as-yet insufficient definitive data regarding the role of NK cell infusions for the treatment of GVHD. There is an active, not yet recruiting, phase 1 clinical trial that seeks to examine the safety of pre-emptive NK cell infusions to reduce the risk (prophylaxis) of both GVHD and disease relapse (NCT03524235). However, there is no ongoing clinical trial to assess NK cells for GVHD treatment. Further investigation is warranted to assess NK cells' role in the prevention and treatment of GVHD.

Myeloid-derived suppressor cells (MDSCs)

MDSCs are a diverse group of immunosuppressive myeloid cells capable of inhibiting both innate and adaptive immune responses. They restrain T cells via multiple mechanisms such as nitric oxide production, reactive oxygen species, expression of arginase 1, and inducible nitric oxide synthase or secretion of IL-10 and transforming growth factor-β [72]. In addition, they suppress NK cells and B-cell proliferation and promote Tregs. They have been mostly investigated for their role in the initiation, progression, and metastasis of tumors and other conditions such as infections, or inflammation. However, they can be mobilized from healthy bone marrow quickly and efficiently to inhibit GVHD and graft rejection. Intriguingly, one of the mechanisms by which ECP is thought to suppress GVHD is by mobilizing MDSCs [72]. Therefore, the interest in MDSCs as treatment for GVHD has grown over the last few years.

A preclinical study by Zhang *et al.* [72] used multiple murine GVHD/GVL models to assess the role of MDSCs. The authors proposed that the induction of NKG2D+ CD8 memory T cells in the donor is needed to eliminate malignant cells while suppressing GVHD and concluded that MDSCs might be used as a cellular therapy for GVHD.

Most human research has studied the role of G-CSF to induce MDSCs in the graft and assess their role against GVHD in the recipient. For example, Fan *et al.* [73] conducted a multicenter randomized clinical trial study to compare the interventions of granulocyte colony-stimulating factor–primed bone marrow (G-BM) with granulocyte colony-stimulating factor–mobilized peripheral blood stem cells (G-PBSC) as the grafts in allo-HSCT for acute leukemia in first complete remission. They found that the G-BM group showed a significantly lower incidence of grade II-IV acute GVHD but similar grade III-IV acute GVHD incidence compared to the G-PBSC group. However, the G-BM group showed a significantly greater probability of GVHD-free/relapse-free survival than the G-PBSC group, and graft content analysis revealed a statistically significant greater proportion of MDSCs in the G-BM than in G-PBSC grafts. The absolute number of MDSCs infused to patients was inversely correlated with the severity of subsequent acute GVHD. Hence, the study concluded that G-BM grafts lead to an improved GVHD-free/relapse-free survival and less GVHD associated with a greater MDSCs content than G-PBSC grafts.

There are other studies with similar findings [74]. However, the complexity of manufacturing these populations for adoptive transfer has been limiting, and there are currently no ongoing clinical trials assessing adoptive transfer of MDSCs for the treatment of GVHD. Nonetheless, this cell population has been associated with a lower incidence of GVHD in both preclinical and clinical studies and further prospective clinical studies are necessary and likely forthcoming to evaluate their therapeutic value in the setting of GVHD after HSCT.

Regulatory B-cells (Bregs)

Bregs (regulatory B10 cells) are a B-cell subset with immunosuppressive and immunoregulatory properties, essential in peripheral

Table 3
Observational and interventional clinical studies related to MSCs for GVHD treatment.

Authors and publication year (reference)	Study design	Primary objective	Number of participants (n)	Intervention	Outcomes at day 28 or as noted*	Conclusion
Ringdén *et al.*, 2006 [49]	Pilot clinical trial	MSCs feasibility	2 children 6 adults	*Ex vivo* MSCs	CR = 75% PR = 0%	MSCs are a very promising treatment for severe SR-aGVHD.
Le Blanc *et al.*, 2008 [42]	Phase 2 clinical trial	Efficacy to ameliorate GVHD after HSCT.	25 children 30 adults	*Ex vivo* MSCs	CR = 54.5% PR = 16 % Assessment time was not specified*	MSCs expanded *in vitro* might be an effective therapy for SR-aGVHD.
von Bonin *et al.*, 2009 [50]	Case series	Efficacy of MSCs in SR-aGVHD	13 adults	BM-derived MSC from unrelated HLA disparate donors	CR = 8% PR = 46%	MSCs have a potential efficacy in the treatment of SR-aGVHD.
Lucchini *et al.*, 2010 [51]	Case series	Describe a multicenter experience of subjects with acute or chronic GVHD treated with MSCs.	11 children	BM-derived MSC from unrelated HLA disparate donors	CR = 23.8% PR = 47.6%	MSCs can be safely used in children, but efficacy seemed to be greater in aGVHD.
Perez-Simon *et al.*, 2011 [44]	Phase 1/2 clinical trial	Feasibility and efficacy of MSCs for the treatment of SR acute or chronic GVHD.	18 adults	MSCs expanded using human serum	CR = 11% PR = 50%	MSCs approach is reasonable in less heavily treated patients for both acute and chronic GVHD.
Prasad *et al.*, 2011 [45]	Clinical trial	Describe the first experience of Remestemcel-L in the treatment of pediatric patients with SR grades III and IV aGVHD.	12 children	Remestemcel-L	CR = 58% OR =17% Assessment at day 60*	MSCs hold potential for the treatment of aGVHD and should be further studied in phase III trials in pediatric and adult patients.
Herrman *et al.*, 2012 [52]	Phase 1 clinical trial	Safety, response rate, and OS in patient with SR acute or chronic GVHD.	19 adults	BM-derived MSCs	CR = 47.4% PR = 31.6% OS = 55%	Further trials are warranted of MSCs with steroid therapy, at the onset of aGVHD prior to steroid resistance.
Ball *et al.*, 2013 [53]	Retrospective cohort	Assess the association between MSCs for SR grade III–IV acute GVHD and survival outcomes.	37 children	BM-derived MSCs	CR = 65% PR = 8%	Multiple MSC infusions are safe and effective for children with SR aGVHD, especially in the early disease course.
Resnick *et al.*, 2013 [54]	Phase 1 clinical trial	Safety in patients with SR acute GVHD	25 children 25 adults	BM-derived MSCs	CR = 34% PR = 32% OS = 56%	MSCs seem to be a promising and safe treatment of GVHD.
Sánchez-Guijo *et al.*, 2014 [55]	Phase 2 clinical trial	Feasibility, safety and efficacy MSCs as a second-line treatment for SR-GVHD	25 adults	Cryopreserved BM–derived MSCs	CR = 46% PR = 25% Assessment at day 60*	MSCs therapy is a safe for patients with SR-aGVHD. This strategy may provide a high rate of OR with a low toxicity.
Muroi *et al.*, 2015 [56]	Phase 2/3 clinical trial	Safety and efficacy for GVHD treatment.	5 children 20 adults	BM-derived MSCs	CR = 24% PR = 36%	Findings suggested MSCs to be effective for SR acute GVHD.
te Boome *et al.*, 2015 [57]	Phase 2 clinical trial	Safety and clinical outcome in patients with SR grade II–IV acute GVHD treated with MSCs	7 children 43 adults	MSCs	CR = 25% PR = not reported OS = 50%	MSCs are associated with a long-term OS of patients with GVHD grade II–IV, a group with high mortality, and do not impair immune responses against viral or GVL.
von Dalowski *et al.*, 2015 [58]	Clinical trial	Clinical outcomes in patients with SR grade II–IV aGVHD treated with MSCs	58 adults	Third-party MSCs expanded in platelet lysate-containing medium	CR = 9% PR = 38%	MSCs plus conventional immunosuppression improved outcome in terms of survival remains to be shown.
Jurado *et al.*, 2017 [59]	Phase 1/2 clinical trial	Safety and feasibility of MSCs in patients with cGVHD.	14 adults	Adipose tissue–derived MSCs (AT-MSCs)	LD: CR = 57% HD: CR = 80%	AT-MSCs may be considered feasible, safe and likely would have an impact on cGVHD.
Dotoli *et al.*, 2017 [60]	Cross-sectional, multicenter, retrospective study	Response rate and OS after treatment with MSCs for SR aGVHD	16 children 30 adults	Ex-vivo BM-derived MSCs from healthy unrelated donors	CR = 6.5% PR = 43.5%	MSCs are safe and should be considered for SR-aGVHD, especially in countries where other second-line agents are less available.

(*continued*)

Table 3 (*Continued*)

Authors and publication year (reference)	Study design	Primary objective	Number of participants (n)	Intervention	Outcomes at day 28 or as noted*	Conclusion
Salmenniemi *et al*., 2017 [61]	Prospective single-arm study	Survival outcomes	8 children 22 adults	BM-derived MSCs	CR = 23% PR = 30%	MSCs showed a good response rate for the treatment of SR-aGVHD. Higher response rates were observed in children.
Bader *et al*., 2018 [43]	Prospective interventional study	Safety and response rate after MSCs infusion.	51 children 18 adults	MSC-Frankfurt am Main (MSC-FFM)	CR = 32% PR = 51%	MSCs were effective in children and adults, suggesting a promising therapy for SR-aGVHD.
Bonig *et al*., 2019 [62]	Prospective interventional study	Safety and response rate after MSCs infusion.	61 children 31 adults	MSC-FFM	OR = 82% OS = 64%	MSC-FFM promises to be a safe and efficient treatment for severe SR-aGVHD.
Kurtzberg *et al*., 2020 [46]	Phase 3 clinical trial	Efficacy and safety of Remestemcel-L in children with high-risk SR-aGVHD.	55 children	Remestemcel-L	CR = 29.6% PR = 40.7%	Robust, prospective evidence of the safety, tolerability, and efficacy of Remestemcel-L as first-line therapy after initial steroid failure in pediatric SR-aGVHD was shown.
Kurtzberg *et al*., 2020 [47]	Phase 3 clinical trial	Efficacy and safety of Remestemcel-L in children with high-risk SR-aGVHD.	241 children	Remestemcel-L	CR = 14.1% PR = 51.3%	This study confirmed the reported clinical and survival benefits of remestemcel-L therapy in children with aGVHD.
Kebriaei *et al*., 2020 [63]	Phase 3 clinical trial	Efficacy of using MSCs in addition to second-line therapy to treat SR-GVHD	27 children 217 adults	Remestemcel-L	Durable CR = 37%	Remestemcel-L was safe and well tolerated. Superior durable CR was not demonstrated.
Soder *et al*., 2020 [64]	Phase 1 clinical trial	Safety, impact on biological markers of aGVHD activity, and clinical outcomes of MSCs	10 adults	Wharton's Jelly-Derived MSCs (WJMSCs)	CR = 40% PR = 30%	Treatment with low- or high-dose MSCs was safe. A clinical improvement was seen that might have been attributable to MSCs infusions.
Purtill *et al*., 2020 [65]	Phase 2 clinical trial	Response rate	66 adults	MSCs + corticosteroids versus corticosteroids alone.	CR = 47% PR = 20% *Assessment at 365 days.	It was decided to terminate the study based on futility, given that a difference in OR favoring the MSCs arm was very unlikely to be observed.
Boberg *et al*., 2020 [66]	Phase 2 clinical trial	Safety and efficacy of MSCs as treatment for SR cGVHD.	11 adults	BM-derived MSCs	OR = 55%	Results highlighted the importance of the MSCs recipient immune phenotype in promoting treatment response
Bloor *et al*., 2020 [67]	Phase 1 clinical trial	Safety and tolerability of MSCs.	15 adults	Induced pluripotent stem cells (iPSCs)-derived MSCs	LD: CR = 13% PR = 50% HD: CR = 57% PR = 29%	The therapeutic application of iPSC-derived MSCs may now be explored in diverse inflammatory and immune-mediated diseases.
Murata *et al*., 2021 [68]	Clinical trial	Efficacy	259 adults 50 pediatrics	BM-derived MSCs (Temcell)	OR = 56%	MSCs are one of the treatment options for SR acute GVHD until a new treatment with survival benefit is developed.

aGVHD, acute graft-versus-host disease; AT-MSCs, adipose tissue–derived mesenchymal stromal cells; BM, bone marrow; cGVHD, chronic graft-versus-host disease; CR, complete response; GVHD, graft-versus-host disease; HD, high dose; IL-2, interleukin 2; LD, low dose; MSCs, mesenchymal stromal cells; MTD, maximum tolerated dose; OR, overall response; OS, overall survival; PR, partial response; SD, stable disease; SR-GVHD, steroid-refractory graft-versus-host disease.

Table 4
Ongoing clinical trials of MSCs for the treatment of GVHD after allo-HSCT.[a]

Study	Status	Target population/ disease	Intervention	Primary outcome	Location
NCT02687646	Not recruiting	18–65 y of age/aGVHD	MSCs from adipose tissue	Safety profile	Spain
NCT03158896	Recruiting	18 y of age or older/SR-GVHD	UC-MSCs	Safety profile	University of Kansas Medical Center, Kansas
NCT05443464	Not yet recruiting	18 y of age or older/SR-aGVHD	Ossium MSCs product	Safety profile	Unavailable
NCT04744116	Recruiting	12–80 y of age/SR-GVHD	MSCs, ruxolitinib	Safety profile OR and death rate at week 4	MD Anderson Houston, TX
NCT00603330	Recruiting	All ages/SR-aGVHD grade II-IV	MSCs	OR at week 4	UZA Edegem, Antwerp, Belgium
NCT04629833	Recruiting	12 y of age older/SR-aGVHD	MSCs	OR at week 4	Grenoble Cedex Grenoble, Lille and Nice, France
NCT05333029	Not yet recruiting	18–75 y of age/GVHD	ECP, MSCs	OR at week 4	University Hospitals Cleveland Medical Center
NCT05531266	Not yet recruiting	All ages/acute GVHD	UC-MSCs	OR at week 4	Tianjin, China
NCT05152160	Recruiting	14–70 y of age/GVHD	UC-MSCs	OR at week 8	Li Yu Shenzhen, Guangdong, China
NCT04692376	Recruiting	18–65 y of age/chronic GVHD	MSCs	OR at week 12	Xin Du Guangzhou, Guangdong, China
NCT04738981	Not yet recruiting	18–70 y of age/GVHD	UC-MSCs	CR at week 4	Peking University People's Hospital Beijing, China

aGVHD, acute graft-versus-host disease; allo-HSCT, Allogeneic hematopoietic stem cell transplant; CR, complete response; GVDH, graft-versus-host disease; MSCs, mesenchymal stromal cells; OR, overall response; SR-GVHD, steroid-refractory graft-versus-host disease; UC, umbilical cord.
[a] Retrieved from clinicaltrials.gov on October 2, 2022.

tolerance characterized by production of IL-10. A role for this B-cell subset has been demonstrated in protection from autoimmune diseases such as systemic lupus erythematous, multiple sclerosis, and GVHD with absent Bregs associated with severe GVHD. Under normal circumstances, Bregs prevent GVHD by blocking the proliferation of pathogenic CD4+ T cells, suppressing the differentiation of T helper 1 cells and other pro-inflammatory lymphocytes [75].

Importantly, the immunoregulatory function of Bregs appears to suppress acute GVHD without affecting GVL activity. This was demonstrated by Hu *et al.* [76] in an observational cohort study in which 74 patients who underwent allo-HSCT (unmanipulated haploidentical and matched sibling donor transplantation) were included. Patients were stratified by the Breg composition of the graft infused. Although confounded by graft composition differences beyond the Breg dose, the cumulative incidence of acute GVHD grades II-IV was

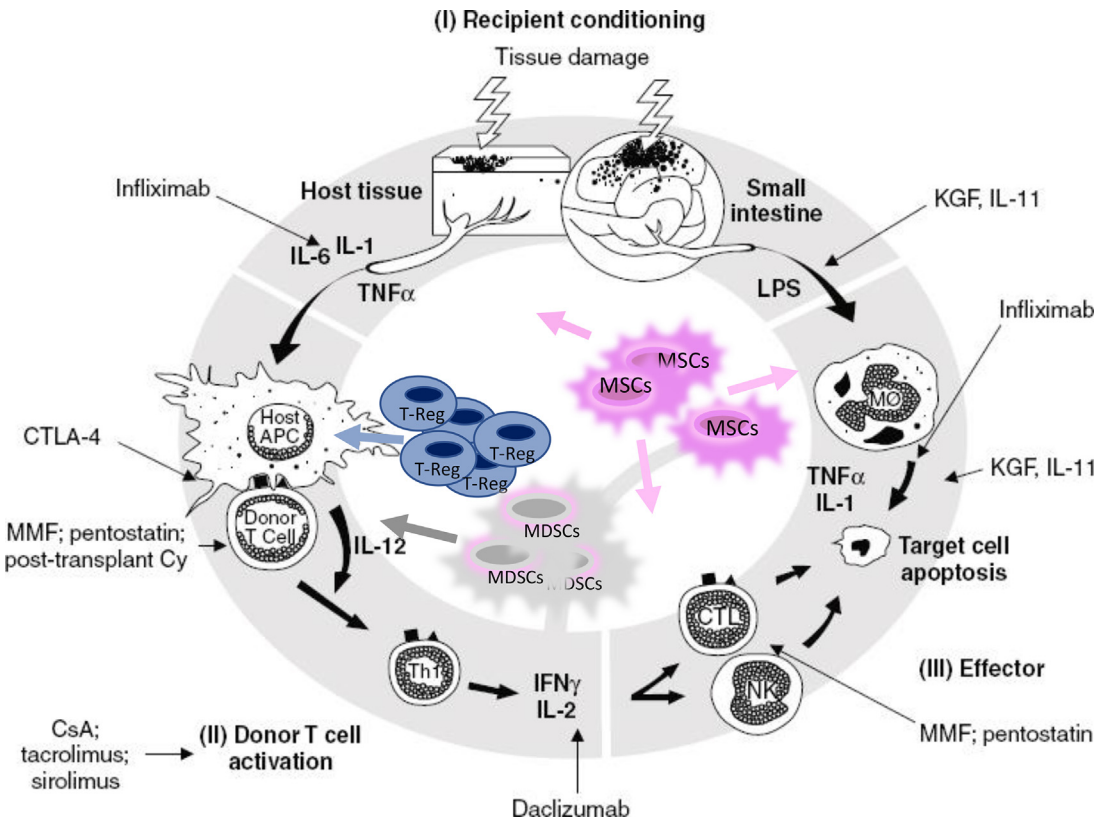

Figure 1. Mechanism of action of the different pharmacologic and cellular therapeutic strategies against GVHD with respect to their targets. Adapted with permission from Ferrara *et al.* [77]. (Color version of figure is available online.)

lower in the high-dose Bregs group without an increased risk of relapse. As yet, no clinical trials have evaluated Bregs as treatment for GVHD, but they are a potential cellular therapy that requires further investigation. Hu *et al.* [76]

There is no strong evidence to understand the relationship between other cellular therapies such as NK cells, MDSCs and Bregs for GVHD treatment and GVHD-related outcomes. Nevertheless, the available evidence suggests that these may be beneficial for the prevention and treatment of GVHD, and additional clinical studies are needed (Figure 1**)** [77].

Feasibility

The last 5 years have seen the first approvals of pharmacologic agents for prevention (abatacept 12/2021) and treatment of acute (ruxolitinib 05/2019) and chronic (ibrutinib 08/2017, belumosudil 07/2021, ruxolitinib 09/2021) GVHD [78]. In the treatment setting, these approvals have been based on trials accruing just 42–65 patients, demonstrating some of the hurdles involved in conducting pivotal/registration trials in this disease. As demonstrated by the trials of MSCs for treatment of GVHD, these challenges become even more significant when combined with the issues around manufacturing of cellular products meeting defined release criteria to allow for predictable *in vivo* activity. As a result, there have only been a handful of cellular therapies explored in a multi-center setting for the treatment of acute or chronic GVHD. While several multicenter trials are now recruiting or poised to recruit (NCT05132166, NCT0060330 and NCT04118556), the issues of patient and product selection and how to deliver even off-the-shelf cellular therapies for treatment of GVHD continues to pose significant challenges that will need to be overcome for cellular therapies to be consistently added to the armamentarium of treatments for GVHD. In addition, these issues are likely to be especially problematic in resource-limited settings.

Recommendations and Future Directions

Despite current pharmacological approaches, non-relapse mortality due to GVHD remains a significant impediment to the success of HSCT. Novel therapies will be essential for improved prevention and treatment of GVHD. The ideal treatment of acute and chronic GVHD would have minimal toxicity and successfully suppress alloreactivity while preserving protection from infection and disease relapse.

As reviewed in this manuscript, several cellular therapeutics are being explored as potential treatments for GVHD. One of the appeals of these approaches is that the safety profile has been promising across a broad array of different cellular types, with few if any identified dose-limiting toxicities.

However, there are multiple challenges that limit the broader use of these approaches. For example, there is still an incomplete understanding of the biology of these cells and their mechanism of action. It also is essential to assess how transplant-related variables such as donor source (unmodified HSCT versus TCD HSCT) or cell infusion strategies in combination with these cellular therapies might influence different clinical outcomes. Another challenge is the heterogeneity in the various cellular products, differences between the mechanism of actions, and their impact on the different cell populations in recipients such as T lymphocytes. Finally, the feasibility of manufacturing these cells in a uniform way has been another limiting factor causing heterogeneity with potentially meaningful impact on the clinical outcomes. In addition, it is unclear whether these cellular therapies could be feasible in resource-limited regions.

Hence, multiple questions remain unanswered concerning cellular therapies and their role in GVHD treatment. What are the optimal products, time of administration and patient population? Are there optimal doses or frequency? Are infusions long-lasting, or should they be administered on a repeating schedule? Are they superior to currently available approaches? Can they be used in combination with other therapies? Validation of the clinical efficacy of cellular products is unclear and will ideally be answered by placebo-controlled trials. These trials must use standardized assessment endpoints regarding safety and treatment response to having comparable primary outcomes among the studies (for example, response at day 28). Biomarkers could also be considered as predictors of treatment response. In addition, participants in these trials need a standardized long-term follow-up to understand whether response rates or outcomes are sustainable and to investigate potential long-term sequelae. Finally, industries should strive to develop manufacturing processes that are easy, feasible to replicate and easy to establish in a variety of locations worldwide. Eventually, meta-analyses could be an essential tool to compare these outcomes and reach a consensus.

Meanwhile, most of the evidence regarding cellular therapies as treatment for GVHD has been with the use of Tregs and MSCs. A commercial MSC product, Remestemcel-L, remains under development. By contrast, no commercial Treg products are yet available. Currently, limited data are available for B-regs, NK cells or MDSCs and their role in treating GVHD. The transplant scientific community will need to harmonize efforts to improve GVHD-related outcomes. Trials with these products will likely benefit from the lessons being learned in trials of Tregs and MSCs. These trials will need to be conducted in well-defined patient populations and take advantage of established predictors of and definitions of outcomes. Therefore, caution must be taken in adopting these new therapeutics in the clinical setting.

Declaration of Competing Interest

JJB: Consulting: Avrobio, BlueRock, Race Oncology, Advanced Clinical, Omeros, Sanofi, Medexus, Equillium, Sobi. AA: served on the safety monitoring committee for Sangamo Therapeutics and has no financial interest in the development of gene therapies. SP: Receives support for the conduct of clinical trials through MSK from AlloVir, Atara, and Jasper. Inventor of IP related to development of third-party viral-specific T cells program with all rights assigned to MSK. CB: Consulting: Zodiac, Amgen, Novartis. SC: ExCellThera: royalties, consulting, shares. DP: Novartis – honoraria, Gilead – honoraria, BMS-Celgene – honoraria, Jazz – honoraria, All honoraria were paid to the author's institution (Fiona Stanley Hospital), not the author. AS: Consultant: Spotlight Therapeutics (2020), Medexus Inc. (2021), Vertex Pharmaceuticals (2021). Research Funding: CRISPR Therapeutics (2021-2022). Honoraria: Vindico Medical Education (2020). Research Collaboration: Magenta Therapeutics (2021-Present). Clinical Trial site-PI: CRISPR Therapeutics (2018-Present), Vertex Pharmaceuticals (2018-Present), Novartis (2019-Present), Magenta Therapeutics (2021-Present). MP-D: Equity: GraphiteBio.

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Author Contributions

Conception and design of the study: Moises Garcia-Rosa, Jaap Jan Boelens and Susan Prockop. Acquisition of data: Moises Garcia-Rosa, Jaap Jan Boelens and Susan Prockop. Analysis and interpretation of data: Moises Garcia-Rosa, Jaap Jan Boelens and Susan Prockop. Drafting or revising the manuscript: All authors. All authors have approved the final article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcyt.2023.02.007.

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