



Published in final edited form as:

Handb Exp Pharmacol. 2022 ; 272: 209–243. doi:10.1007/164_2021_544.

Immune Suppression in Allogeneic Hematopoietic Stem Cell Transplantation

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Keywords

Allogeneic hematopoietic stem cell transplantation; acute graft-versus-host disease; immune suppression

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a curative modality for high-risk malignancies, hematologic disorders, immunologic disorders, and metabolic disorders¹. Fundamentally, HSCT results in the complete or partial replacement of the hematopoietic system. The procedure is performed by first conditioning the recipient with chemotherapy and/or total body irradiation followed by the infusion of donor HSCs. Conditioning serves to make physical space in the recipient bone marrow for the new HSC graft and to suppress the recipient's immune system to prevent graft rejection. Following stem cell engraftment, the donor graft repopulates the hematopoietic and immunologic compartments.

There are two main categories of HSCT: autologous and allogeneic. In autologous HSCT, the hematopoietic compartment is rescued with a cryopreserved autologous HSC product harvested from the recipient prior to conditioning. Autologous HSCT is typically used to reconstitute hematopoiesis following consolidative, high-dose, myeloablative chemotherapy regimens for lymphomas and various solid tumors thereby overcoming the hematopoietic dose-limiting toxicity of these consolidative regimens.

In contrast to autologous HSCT, the stem cell graft in allogeneic HSCT is derived from a different person than the recipient, which makes allogeneic HSCT useful for treating hematologic, immunologic, and metabolic disorders. Because the graft donor and recipient are different people in allogeneic HSCT, polymorphic antigens will differ between the donor and recipient. These polymorphic antigens are recognized by donor allogeneic T cells, which are the primary drivers of alloimmunity. Alloimmune reactions are beneficial when the donor alloimmune response is directed against polymorphic antigens present on tumor

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cells. This antitumor response is termed the graft-versus-tumor (GVT) effect and represents one of the first immunologic therapies for cancer. However, alloimmune reactions can also be directed against polymorphic allogeneic antigens present on host tissues resulting in acute graft-versus-host disease (aGVHD). These activated allogeneic antigen-responsive T cells then drive the immune-mediated damage of the main aGVHD target organs in the recipient, namely the skin, liver, and gastrointestinal (GI) tract². Due to the risk of aGVHD, nearly all allogeneic HSCT recipients receive aGVHD prophylaxis with immunosuppressive therapies. Despite prophylaxis, aGVHD occurs in 30–50% of patients and remains the major life-threatening complication of allogeneic HSCT². Herein, we discuss the pathophysiology of aGVHD, the immunosuppressive therapies used to prevent and treat aGVHD, and how best to mitigate the myriad off-target and on-target side effects of these therapies, including infection and relapse.

CLINICAL FEATURES OF aGVHD

The main organs affected by aGVHD are the skin, liver, and GI tract. In rare instances, the lungs, central nervous system, and retinas are also affected³. Acute GVHD typically manifests within the first 100 days after transplantation; however, it can occur later³. The risk of aGVHD is increased by HLA-mismatched grafts, advanced age of the recipient or donor, male recipients of female donors, unmanipulated peripheral blood stem cell grafts relative to bone marrow or umbilical cord blood grafts, and with myeloablative conditioning regimens relative to reduced intensity regimens^{3–6}.

The skin is typically the first organ affected by aGVHD². Signs of skin aGVHD include an erythematous maculo-papular rash that can advance to blisters and ulceration^{2,3}. Early skin aGVHD has a predilection for the palms, soles, ears, neck, and dorsal surfaces of the extremities and malar regions^{2,3}. Histology of skin aGVHD typically reveals apoptosis at the basal membrane of the epidermal layer, dyskeratosis, exocytosis of lymphocytes, satellite lymphocytes adjacent to dyskeratotic epidermal keratinocytes, and perivascular lymphocytic infiltration in the dermis³. These histopathological findings often overlap with those of drug reactions and infectious etiologies, thereby limiting the usefulness of skin biopsy for the diagnosis of cutaneous aGVHD^{7,8}. Upper GI aGVHD typically manifests with nausea, weight loss, and anorexia^{2,3}. Patchy ulcerations and flattening of surface epithelium are typically seen on histopathology³. Lower GI aGVHD manifests as watery and/or bloody diarrhea with or without crampy abdominal pain^{2,3}. Apoptotic bodies and abscesses in the epithelial crypts are diagnostic on histopathology of endoscopic biopsies^{2,3}. Liver aGVHD clinically manifests with elevated total bilirubin with or without jaundice^{2,3}. Pathology is notable for lymphocytic infiltration near port veins and bile ducts with bile duct loss occurring in advanced lesions^{2,3}.

The severity of aGVHD is staged within each of the primary target organs: skin, liver, and gut^{9,10}. These stages are then combined into an overall grade^{9,10}. The skin is staged from 0 to 4 based on the percent of body surface area involvement (stage 0, no rash; stage 1, rash <25% body surface area (BSA); stage 2, 25–50% BSA; stage 3, generalized erythroderma or rash >50% BSA; stage 4, generalized erythroderma plus bullous formation and desquamation >5% BSA). Liver GVHD is staged based on the serum total bilirubin

level (stage 0, <2mg/dL; stage 1, 2–3 mg/dL; stage 2, 3.1–6 mg/dL; stage 3, 6.1–15 mg/dL; stage 4, >15 mg/dL). The GI tract is staged based on the volume of stool output per day in adults (patients >50kg in weight), or stool output per kilogram bodyweight in children (stage 0, <500 mL/day or <30 mL/kg; stage 1, >500 mL/day or >30 mL/kg; stage 2, >1000 mL/day or >60 mL/kg; stage 3, >1500 mL/day or >90 mL/kg; stage 4, severe abdominal pain with or without ileus, or grossly bloody stool, regardless of stool volume). Isolated acute upper GI GVHD confirmed by upper GI biopsy is considered stage 1.

The Glucksberg Scale is the most widely used system for grading aGVHD and reflects the fact that the GI tract is the target organ most associated with nonrelapse mortality^{10,11}. Mild, grade I acute GVHD, consists of stage 1 or 2 skin involvement without liver or GI involvement. Moderate, grade II GVHD, consists of stage 3 skin involvement or stage 1 liver or GI involvement. Grade III, severe, acute GVHD consists of stage 0–3 skin, with stage 2–3 liver or GI involvement. Finally, grade IV, very severe and life-threatening acute GVHD, consists of stage 4 skin, liver or GI involvement. Acute GVHD occurs in 30–50% of all allogeneic HSCT recipients and is severe (grade III-IV) in approximately 15%³. While the Glucksberg Scale is widely employed clinically, recent studies have found that it does not optimally predict outcomes. Newer algorithms using clinical criteria or biomarkers are showing promise and are being explored as potentially useful early parameters to intervene upon in order to improve treatment response and survival in high risk aGVHD^{11–15}.

INFLUENCE OF DONOR GRAFT, MHC MATCHING, AND CONDITIONING ON aGVHD

Acute GVHD is understood as a donor allogeneic T cell-dependent response to disparate histocompatibility antigens in an immunocompromised host. The recipient must be immunocompromised, typically as a result of conditioning, or the host immune system will prevent the donor allogeneic T cells from engrafting and responding to these disparate antigens. Genetic polymorphisms between the donor and recipient are responsible for these disparate antigens, of which the histocompatibility antigens are the most influential. Histocompatibility antigens are designated as either major (MHC) or minor (miHA) based on their degree of immunogenicity. The MHC complex, also referred to as the human leukocyte antigen (HLA) system in humans, is located on the short arm of chromosome 6. MHC class I antigens (HLA-A, -B, and -C) are expressed on the surface of nearly all nucleated cells and mainly present endogenous peptide antigens to CD8 cytotoxic T cells. MHC class II antigens (HLA-DR, -DQ, and -DP) are mainly expressed on the surface of hematopoietic professional antigen presenting cells (B cells, monocytes, macrophages, and dendritic cells). However, many other hematopoietic-derived, epithelial, endothelial, and stromal cell populations can also express MHC class II, especially under inflammatory conditions^{3,16}. MHC class II molecules present mainly exogenous peptide antigens to CD4 T cells. In contrast to MHC molecules, miHAs are polymorphic peptides bound to and presented by MHC molecules. They are generally ubiquitously expressed, but can differ in their tissue expression¹⁷. This difference in expression among tissues may be one of the reasons why aGVHD predominantly involves the skin, liver, and gut. Some miHAs are also selectively expressed in the hematopoietic system and may be more potent targets

of graft-versus-tumor rather than graft-versus-host responses¹⁷. Minor histocompatibility antigen mismatches are most relevant to clinical aGVHD because the majority of clinical allogeneic transplants are MHC-matched.

The risk of acute GVHD is directly related to the degree of histocompatibility antigen mismatch³. For this reason, the optimal HSC donor is an MHC-matched related donor (MRD). Related donor grafts presumably have better outcomes in part due to less miHA mismatches. Unfortunately, aGVHD still occurs in 40% of patients who receive fully-matched grafts and immunosuppressive prophylaxis².

Most centers define an MHC-matched graft as one that is matched at the allelic level for HLA-A, -B, -C, and -DRB1 with minor clinical benefit for allelic matching at HLA-DQ, HLA-DP, and DR3/4/5¹⁸. The minimal amount of MHC matching varies based on the HSC source. For bone marrow and peripheral blood-derived grafts, 8/8 matches are ideal, but 7/8-mismatched grafts can be used when better matched donors are unavailable¹⁸. However, aGVHD and mortality are increased with mismatched donors compared to matched donors, and the aGVHD prophylaxis for these donors is typically more immune suppressive^{4,5,19}. Engraftment of umbilical cord blood HSCs is routinely achieved with greater than or equal to a 4/6 match (HLA-A, -B, -DR) using antigen-level matching for HLA-A and -B and allelic matching at HLA-DR, but mortality is lower when two or greater allelic mismatches are present within HLA-A, -B, -C, or -DR^{18,20,21}. Haploidentical donor grafts, as their name implies, can successfully engraft when the donor and recipient are half-matched. Acute GVHD prophylaxis for haploidentical donor transplantation typically employs post-transplant cyclophosphamide (PTCy) in addition to calcineurin-based regimens used for MRD transplantation²².

The primary sources for donor stem cell grafts are the bone marrow and peripheral blood. Apheresis is used to harvest peripheral blood stem cell (PBSC) grafts following stem cell mobilization using hematopoietic growth factors such as granulocyte colony stimulating factor (G-CSF). Hematopoietic stem cells can also be obtained from umbilical cord blood²³.

The T cell content of an HSC graft directly correlates with the risk of aGVHD. Peripheral blood-derived grafts carry the greatest T cell load followed by bone marrow and then umbilical cord blood grafts^{3,5,24}. Typically, HSC grafts are infused without altering their immune cell content. However, many approaches are being explored to reduce the T cell load of HSC grafts prior to infusion. These include positive selection of CD34⁺ stem cells, depletion of $\alpha\beta$ T cells, and depletion of naïve T cells, which are naïve to their cognate antigen and are more potent inducers of aGVHD relative to antigen-experienced memory T cells²⁴. One benefit of these approaches is that they often require less immunosuppressive aGVHD prophylaxis. However, because alloimmune T cell-mediate GVT and aGVHD are closely linked, relapse rates are often higher with T cell-depleted grafts²⁴. T cells are also critical for engraftment and immune recovery; therefore, T cell-depleted grafts often have higher rates of graft failure and infections²⁴.

Prior to administration of the HSC graft, recipients typically receive conditioning therapy to eradicate their malignancy and promote HSC engraftment. The intensity of conditioning

regimens varies based on each patient's disease type, disease status, overall health, and donor stem cell source^{3,4}. Full intensity, myeloablative conditioning regimens are typically associated with a greater risk of aGVHD^{4,25}. This is thought to be due to greater tissue injury from these full intensity regimens. The tissue injury causes the release of danger associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs) that then activate antigen presenting cells resulting in the secretion of pro-inflammatory cytokines and the robust activation of allogeneic T cells³.

CHRONIC GVHD

Chronic GVHD (cGVHD) is a significant risk factor for nonrelapse mortality in patients two years or greater post allo-HSCT²⁶. It is classically defined as occurring greater than 100 days post-HSCT; however, it can occur earlier and present as an overlap syndrome with features of both acute and chronic GVHD. Chronic GVHD occurs in 30–70% of allo-HSCT recipients. It can arise *de novo* (i.e. in the absence of any prior aGVHD); however, it more commonly arises progressively (i.e. aGVHD transitions into cGVHD) or following a period of quiescent aGVHD (i.e. prior aGVHD resolves and then cGVHD develops)². Virtually every organ system can be affected by cGVHD, which resembles an “autoimmune syndrome”^{26,27}. Common manifestations include lichen planus-like skin lesions, sclerosis, myositis, fasciitis, vulvo-vaginitis, bronchiolitis obliterans (BO), sicca syndrome, and damage of the gastrointestinal tract and liver^{2,26,27}. Diagnosis, staging, and response grading of cGVHD are based on the the National Institutes of Health Consensus Criteria^{28,29}. Risk factors include prior aGVHD, HLA-mismatched grafts, peripheral blood stem cell grafts relative to bone marrow grafts, older age of the recipient or donor, and transplantation of female grafts into male recipients⁵.

The immunobiology of cGVHD is complex and distinct from that of aGVHD. Briefly, it can be conceptualized in three phases: 1) inflammation causing tissue damage, 2) chronic inflammation leading to thymic injury as well as B and T cell dysregulation, and 3) tissue repair and often debilitating fibrosis^{16,26}. A more detailed description of cGVHD immunobiology and management with immune suppression are outside the scope of this review. However, aGVHD is one of the greatest risk factors for cGVHD, and the immunosuppressive agents used to prevent and treat cGVHD often overlap with aGVHD^{26,27,30}. Therefore, we will point out those immunosuppressive agents used for both acute and chronic GVHD.

IMMUNOBIOLOGY OF aGVHD

The pathophysiology of aGVHD comprises a donor allogeneic T cell-dependent response to disparate histocompatibility antigens that results in the induction of pro-inflammatory cytokines and cellular effectors that damage target organs. Conceptually, it can be thought of as a destructive, unchecked immune response to foreign antigens. Acute GVHD pathogenesis consists of three phases. In phase I, tissue injury from conditioning therapy causes inflammatory cytokine production and activation of APCs. In phase II, donor allogeneic CD4 and CD8 T cells recognize alloantigens, become activated, expand, and differentiate into effector T cells. In phase II, effector T cells and additional inflammatory

mononuclear subsets traffic to aGVHD target organs and cause direct cell-mediated or indirect inflammatory cytokine-mediated tissue damage³¹. Similar to an immune response to a pathogen, the immunobiology of aGVHD consists of triggers, sensors, mediators, effectors, amplifiers, and modulators³². While these frameworks are useful to conceptualize aGVHD pathophysiology, it is important to understand that aGVHD is a complicated systemic process with still many unknowns. Furthermore, a majority of aGVHD pathophysiology is based on murine studies. Therefore, it is worth noting that these studies are limited by differences in genetic heterogeneity, basic physiology, immune responses, microbiomes, environmental exposures, and HSCT procedures between laboratory mice and humans. Nonetheless, the rich understanding of aGVHD pathophysiology in murine models is the foundation of many immunosuppressive therapies for aGVHD prevention and treatment.

Tissue injury and inflammation from pre-transplant conditioning (aGVHD triggers and sensors):

Tissue damage from conditioning is the earliest trigger of aGVHD. Damaged tissues release endogenous DAMPs, including uric acid and adenosine triphosphate (ATP)^{3,33,34}. In the gut, damaged epithelium allows for the translocation of exogenous PAMPs, such as lipopolysaccharide (bacterial component), CpG oligodeoxynucleotides (viral DNA), and α -mannan (fungal component)³. Alarmin molecules (IL-1 α , IL-33, and HMGB1) are also released. DAMPs, PAMPs, and alarmins are then recognized by pattern recognition receptors (PRRs) (e.g. NOD-like receptors and Toll-like receptors) and alarmin receptors in host tissues¹⁶. Ligand-bound PRRs and alarmin receptors initiate signaling pathways (e.g. NF- κ B) that activate cytokine (e.g. TNF α , IL-1 β , IL-6, IL-33, IL-12, IL-23, type I IFNs) and chemokine (e.g. CCL5) production^{3,16,35}. These inflammatory cytokines and chemokines recruit myeloid cells including monocytes and neutrophils, which cause further tissue damage, particularly in the GI tract, through their production of reactive oxygen species^{3,16,35}.

APCs are the main sensors of aGVHD. The inflammatory environment created by the conditioning regimen activates host APCs (e.g. dendritic cells and macrophages)^{3,16}. Activated APCs increase allo-antigen presentation, upregulate co-stimulatory molecules, and secrete inflammatory cytokines^{3,16}. In this way, activated APCs provide the primary, secondary, and tertiary signals needed for the activation of donor allogeneic T cells, which are the primary mediators of aGVHD. Host APCs, particularly dendritic cells (DCs), are thought to be the most potent activators of allo-T cells early post-transplant. However, donor APCs in general and donor CD103⁺ DCs specifically migrate to lymphoid tissues where they also activate allo-reactive T cells that potentiate aGVHD^{16,36}. Allogeneic antigens are also presented by non-hematopoietic host tissues³⁷⁻³⁹. For example, damage from conditioning induces IL-12 secretion from intestinal macrophages that then drives the production of IFN- γ from intestinal lymphocytes. IFN- γ then enhances MHC-II expression on intestinal epithelial cells thereby promoting CD4 T cell-mediated aGVHD³⁸.

Stimulation, differentiation and proliferation of effector T cells (aGVHD mediators):

Donor allo-reactive T cells are the primary mediators of aGVHD. Upon infusion, they enter a lymphopenic, inflamed host, which promotes their profound proliferation¹⁶. In murine models, naïve (CD62L⁺ CD45RA⁺ CCR7⁺) T cells (i.e. antigen-inexperienced) are far more likely to cause aGVHD than memory T-cells^{16,40}. However, human recipients of naïve T cell-depleted grafts still develop aGVHD^{24,41}. Proliferating naïve T cells then traffic to lymph nodes where they become activated by disparate histocompatibility antigens on APCs. APCs also provide important secondary activation signals to these T cells through co-stimulatory molecules. Co-stimulatory pathways such as CD28, ICOS, OX40, and 4-1BB lower T cell activation thresholds, augment cytokine production, inhibit apoptosis, and support effector T cell metabolism³. Similarly, the Notch ligand DLL4 expressed on non-hematopoietic stromal cells, also promotes allogeneic T cell-driven aGVHD^{35,42}.

Signal transduction downstream of the T cell receptor and co-stimulatory receptors starts with receptor-proximal phosphorylation of signaling molecules^{43,44}. This then promotes the activation of phospholipase C which hydrolyzes phosphatidylinositol bisphosphate (PIP₂) to yield diacylglycerol (DAG) and inositol trisphosphate (IP₃). DAG recruits a number of downstream signaling molecules including protein kinase C- θ (PKC θ) that results in the activation of the mitogen-activated protein kinase (MAPK) cascade and culminates in the activation of the transcription factor AP-1. PKC θ also induces a signaling pathway leading to the activation of the transcription factor NF- κ B. Meanwhile, IP₃ causes calcium channels to open thereby raising the cytoplasmic calcium concentration. This promotes the activation of the protein phosphatase calcineurin, which dephosphorylates the transcription factor nuclear factor of activated T cells (NFAT). The end result of TCR signal transduction is the activation of the transcription factors NFAT, AP-1, and NF- κ B that induce the expression of a number of genes that promote the activation and proliferation of T cells including IL-2^{43,44}.

Effector CD4 and CD8 T cells differentiate into helper (Th) and cytotoxic (Tc) subsets characterized by the cytokines they produce and the expression of subset-specific transcription factors^{16,45}. The inflammatory cytokine milieu present post-HSCT generally polarizes CD4 helper and CD8 cytotoxic T cells towards the inflammatory Th1/Th17 and Tc1/Tc17 subsets, respectively^{16,45}. Th1/Tc1 polarization is promoted by high levels of IL-12 and IFN- γ , and Th17/Tc17 polarization is promoted by high levels of IL-6 in combination with TGF β . IL-6 also inhibits the induction of Tregs. In contrast to IL-12 and IFN γ , IL-4 levels, which support Th2/Tc2 differentiation, are generally minimally elevated post allogeneic HSCT. Th1/Tc1 are characterized by the production of the inflammatory cytokines IL-2, IFN- γ and TNF- α whereas Th17/Tc17 produce IL-17 and IL-21^{16,45}. Th1/Tc17 and Tc1/Tc17 cells promote aGVHD. By contrast, Th2/Tc2 (secrete IL-4, IL-5, and IL-13) and Tregs (secrete IL-10 and TGF β) ameliorate aGVHD^{16,45}. However, exceptions to these generalizations exist at least in part due to contextual differences among models. For example, IFN- γ is a characteristic cytokine of Th1 cells, and it is cytotoxic to intestinal epithelial cells⁴⁶. Despite this, its absence in donor T cells is protective when mice are conditioned with low-dose irradiation and detrimental when conditioned with high-dose irradiation⁴⁷. This discrepancy was shown to be due in part to IFN- γ 's ability

to protect against Th2-mediated lung damage^{16,45}. Nevertheless, donor T cells deficient for the Th1-specific transcription factor, T-bet, caused less severe aGVHD⁴⁸. In addition to model-dependent effects of T cell differentiation on aGVHD, the polarization of helper T cell subsets is reciprocally regulated. Disrupting this regulation in model systems skews helper T cell polarization, cytokine production, and T cell migration such that different organs are targeted depending on which helper T cell differentiation pathway is blocked⁴⁹.

Helper T cell subsets differentially express chemokine receptors that govern their trafficking to target tissues⁴⁵. Th1 cells express CCR5 and CXCR3, which aids their trafficking to the gut and liver, respectively⁴⁵. Th17 cells express CCR6 promoting trafficking to the skin, and Th2 cells express CCR4 allowing them to traffic to the lungs⁴⁵. This differential expression of chemokine receptors on inflammatory T cell subsets may contribute to the gut, liver, and skin being the primary aGVHD target organs. As a further example of how T cell trafficking influences aGVHD, colon-derived donor DCs migrate to mesenteric lymph nodes where they activate donor T cells and imprint them with gut-homing expression of $\alpha 4\beta 7$ integrin³⁶. This leads to the migration of allogeneic T cells into the GI tract where they cause fulminant disease³⁶.

Tissue damage by effectors and inflammatory cytokines (aGVHD effectors and amplifiers):

The effector phase leading to GVHD target organ damage is mediated by inflammatory monocytes, cytolytic cellular effectors (e.g. CD8 and CD4 T cells), inflammatory cytotoxic cytokines (e.g. IL-1 β , TNF α , IFN- γ), and reactive oxygen species (ROS)^{3,16}. GVHD organ damage caused by these effector mechanisms is further amplified by a vicious cycle of tissue damage, inflammation, recruitment of cellular effectors, and secretion of cytotoxic cytokines^{3,16}.

CD4 and CD8 T cells are the main cellular effectors of aGVHD. They are typically donor in origin, but recent evidence suggests that recipient tissue resident memory T cells may also cause tissue damage^{50,51}. T cells typically kill target cells via contact-dependent mechanisms including activation of perforin-granzyme, Fas–FasL (CD95-CD95L), or TNFR-TNF-related apoptosis-inducing ligand (TRAIL) pathways^{52,53}. Perforin and granzyme are stored in the cytotoxic granules of cytotoxic T lymphocytes (CTLs) and are secreted upon recognition of target cells. Perforin forms pores in target cells through which granzyme passes. Granzyme then induces apoptotic death in target cells by releasing mitochondrial cytochrome C. Fas clustering on the surface of target cells is induced by binding to FasL on T cells, resulting in the formation of a death-inducing signal complex and the triggering of apoptosis on target cells⁵². Other CTL killing mechanisms involve TNF death ligand receptor–triggered apoptosis by activation of the TNF/TNFR, TRAIL, TNF-related weak inducer of apoptosis (TWEAK), and lymphotoxin β (LT β)/LIGHT pathway³².

Inflammatory pathways do not require cell-cell contact to kill target cells. Instead, target cell damage is caused by cytotoxic cytokines (TNF α and IFN γ) and ROS released by allogeneic T cells and inflammatory monocytes, respectively^{3,54}. It is important to note that both the cell-mediated and inflammatory cytotoxic cytokine-mediated effector pathways are important for GVL effects as well as negative feedback on inflammatory components

driving aGVHD^{16,52}. Therefore, the utility of therapeutically targeting aGVHD effector mechanisms is uncertain.

Tissue repair and anti-inflammatory mechanisms (aGVHD modulators):

There are many immune cell-related and non-immune cell-related mechanisms that modulate aGVHD pathophysiology and contribute to tissue repair. For instance, activated allogeneic T cells not only express co-stimulatory receptors but also co-inhibitory receptors that attenuate allo-T cell responses and suppress aGVHD such as CTLA-4, PD-1, BTLA, LIGHT, LAG3, TIGIT, and VISTA^{3,16}. In addition, many cytokines secreted by activated T cells (e.g. IFN γ , IL-12, IL-22, IL-10, TGF β , and IL-2) have both pro- and anti-aGVHD effects depending on the context and model system^{3,16,35}. APCs also have dual effects on aGVHD that vary by context and the subset examined. As an example, both host and donor DCs promote aGVHD whereas host CD8⁺ DCs and donor pre-plasmacytoid DCs inhibit aGVHD⁵⁵. Furthermore, the ability of dendritic cells to promote inflammatory or tolerogenic immune responses can be modified. For instance, co-transplantation of ex vivo-derived regulatory DCs inhibits aGVHD in murine models⁵⁶. One promising way of promoting a tolerogenic DC phenotype in vivo is to administer histone deacetylase inhibitors (HDACi), which improve aGVHD in both pre-clinical and clinical studies^{57,58}.

Similar to DCs, macrophages are an APC that also regulate aGVHD in complex ways⁵⁹. Blocking their recruitment to target organs inhibits aGVHD, and the anti-aGVHD activity of corticosteroids appears to be in part due to the inhibition of macrophages^{60,61}. However, other studies have shown that host macrophages attenuate aGVHD in murine models^{62,63}. The influence of inflammatory M1 macrophages relative to anti-inflammatory M2 macrophages on aGVHD is also complex. One study found an elevated M2 macrophage gene signature in colon biopsies from steroid refractory aGVHD patients⁶⁴. By contrast, G-CSF-mobilized HSCT grafts with higher levels of M2 macrophages were associated with less subsequent aGVHD⁶⁵.

A subset of monocytic and granulocytic myeloid cells, termed myeloid derived suppressor cells (MDSC), are highly immune suppressive^{3,66}. Adoptively transferred MDSCs promoted tolerogenic Th2 and Treg responses thereby suppressing murine aGVHD^{66-70,70-72}. However, MDSCs can lose their suppressor function by inflammasome activation when in pro-inflammatory environments^{73,74}. Due to this, repeat MDSC infusion is often required to control aGVHD in murine models.

Mesenchymal stromal cells (MSC) may also be useful for the treatment of aGVHD. MSCs are typically derived from bone marrow, umbilical cord blood, or adipose tissue. They express CD73, CD90, and CD105 and lack expression of CD34, CD45, CD14, CD11b, CD79a, CD19, and HLA-DR^{66,75}. They are further defined by their ability to adhere to tissue culture plates and differentiate into osteoblasts, adipocytes, and chondroblasts. MSCs express little if any MHC-I or MHC-II allowing them to be administered across HLA barriers. These cells possess immunosuppressive capabilities in inflammatory environments via a variety of mechanisms including apoptotic death of the MSCs by host immune cells. The apoptotic MSCs are then phagocytosed which promotes the secretion of anti-inflammatory mediators that regulate both innate and adaptive immune cells. Due to

their limited survival in the host, multiple infusions are required^{66,75}. A number of small heterogeneous studies showed variable responses of steroid refractory aGVHD (SR-aGVHD) to MSC therapy^{66,75}. One multicenter, randomized controlled trial did not meet its primary endpoint of improved durable complete remission⁷⁶. However, overall responses were significantly higher in pediatric and high-risk patients. MSC efficacy in pediatric SR-aGVHD was also shown in a prospective, single-arm, phase 3 study⁷⁷. Importantly, MSCs are safe and well tolerated^{66,75}. Despite clinical trials showing inconsistent results, they are increasingly being used for aGVHD especially in the steroid-refractory setting.

Regulatory T cells are classically defined as CD4⁺ FOXP3⁺ CD25⁺ cells with immunosuppressive capacity. CD8⁺ and FOXP3⁻ regulatory T cell subsets have also been described, but the role of CD4⁺ FOXP3⁺ CD25⁺ Tregs is far more established in aGVHD¹⁶. CD4⁺ FOXP3⁺ CD25⁺ Tregs arise directly following thymic maturation or are induced in the periphery from CD4 T cells⁷⁸. Acute GVHD is associated with deficient Treg reconstitution and reduced Treg function in pre-clinical and clinical studies^{78,79}. Enhancing or adoptively transferring donor Tregs in pre-clinical models increases the ability of Tregs to suppress conventional allogeneic T cells and prevent or mitigate aGVHD⁷⁸⁻⁸¹. In early-phase clinical trials, adoptive transfer of Tregs appears safe and effective for aGVHD prevention without causing greater leukemia relapse⁸²⁻⁸⁵. The ability of Tregs to treat clinic aGVHD remains to be determined⁸⁶. Major limitations of adoptive Treg therapy include that their ex vivo expansion is challenging and that they often convert to non-regulatory conventional T cells in inflammatory environments^{16,78,79}. Therefore, another approach has been to enhance Treg recovery and activity in vivo by taking advantage of their increased IL-2 receptor expression and relative heightened dependence on IL-2 for survival compared to conventional T cells. Consistent with this, low-dose IL-2 therapy preferentially expanded Tregs relative to conventional T cells and mitigated chronic GVHD in a phase 1 clinical trial^{87,88}. Calcineurin inhibitors (CNIs), which are commonly used for aGVHD prophylaxis, inhibit IL-2 production and may hinder Treg recovery post-HSCT⁸⁹. However, the mTOR inhibitor, rapamycin, has less of an effect on IL-2 production, and when combined with low-dose IL-2, it expanded Tregs in vivo⁸⁹⁻⁹¹.

Alpha-1-antitrypsin (AAT) is a serine protease inhibitor produced by the liver and is lost through the GI tract especially with GI aGVHD⁹². In murine models, AAT administration was effective at preventing and treating aGVHD^{93,94}. The anti-aGVHD mechanism of AAT is not clear, but may involve promoting Treg recovery and altering inflammatory cytokine production⁹³⁻⁹⁵. A phase 2 clinical trial showed promising responses in steroid-refractory acute GVHD⁹⁵.

B cells are lymphoid cells best known for their production of antibodies and their ability to present antigens. The role of B cells in aGVHD is nuanced. B cell depletion prior to HSCT in mice and humans inhibited aGVHD^{76,96-102}. Human HSCT grafts with high numbers of B lymphocytes correlated with an increased incidence of aGVHD.¹⁰³ In contrast to these studies suggesting that B cells aggravate aGVHD, studies in mice also showed that B cells inhibit aGVHD by producing the anti-inflammatory cytokine IL-10¹⁰⁴. Co-transfer of regulatory B cells also attenuated murine aGVHD^{16,105}. In humans, grafts with a high

content of B cell progenitors are associated with less aGVHD¹⁰⁶. Altogether, these studies suggest that B cells likely modulate aGVHD in a context and subset-dependent manner.

NK cells are innate lymphoid cells with important anti-tumor and anti-microbial properties. They are the first donor lymphoid cell to recover post-HSCT¹⁰⁷. Their effect on aGVHD is also variable and likely depends on incompletely understood contextual factors. Early studies in mice and humans suggested that NK cells promoted aGVHD^{107–110}. However, subsequent studies suggested that NK cells regulated alloimmune T cells via direct cytotoxic mechanisms resulting in less aGVHD^{107,111–113}. By contrast, recent studies also suggest activated NK cells administered at later time points post-HSCT may augment aGVHD via inflammatory cytokine-mediated indirect activation of alloimmune T cells^{107,114–117}. Nonetheless, most clinic studies of adoptively transferred NK cells did not increase the incidence of aGVHD^{107,118–120}.

Invariant natural killer cells (iNKT) are CD3⁺, CD4⁺ or CD4⁻ cells that express NK cell markers and an invariant $\alpha\beta$ TCR. Invariant NKT cells respond to lipid molecules presented by the non-polymorphic MHC-I-like CD1d molecule⁶⁶. When activated, these cells promote tolerance by secreting IL-4 and IL-13^{66,121}. Human grafts with high iNKT cells numbers are associated with a lower incidence of aGVHD¹²². In mice, iNKT cells protected against aGVHD^{66,121,123,124}. In humans, the iNKT agonist RGI-2001, decreased the incidence of aGVHD¹²⁵. These data overall suggest that targeting iNKT cells may be a promising approach for preventing aGVHD.

Mucosal-associated invariant T (MAIT) cells express a semi-variant TCR that recognizes microbial vitamin B biosynthesis intermediates presented by the monomorphic MHC-I-related molecule, MR1¹²¹. Mouse studies show that recipient MAIT cells reduce GI aGVHD by promoting intestinal barrier function in an IL-17-dependent manner¹²⁶. The association of MAIT cell reconstitution and clinical aGVHD is variable and requires further study^{66,127–129}.

Gamma-delta (γ/δ)T cells are unconventional T cells activated by phospho-antigens¹²¹. Their role in aGVHD is uncertain. Murine models demonstrated that both host and recipient γ/δ T cells exacerbated aGVHD^{130,131}. However, the clinical evidence for human γ/δ T cells exacerbating aGVHD is variable¹²¹. Consistent with a minimal contribution of human γ/δ T cells to aGVHD, α/β T cell-depleted grafts, which are enriched in γ/δ T cells, are well-tolerated^{132,133}.

Innate lymphoid cells (ILC) lack rearranged antigen receptors and share a common progenitor with NK cells. ILCs are classified into ILC1, ILC2, and ILC3 subsets that possess cytokine repertoires similar to that of Th1, Th2, and Th17 cells^{66,134}. Secretion of IL-22 by recipient ILC3 cells protected intestinal stem cells from allogeneic T cell-mediated damage and ameliorated aGVHD in mice¹³⁵. Transfer of donor ILC2 cells treated established murine aGVHD by activating anti-inflammatory MDSCs in an IL-13-dependent manner¹³⁶. Delayed ILC reconstitution in humans has also been associated with a higher risk for aGVHD¹³⁷. A clear role for ILC1 cells in the pathogenesis of aGVHD has not yet been determined.

The gut microbiome is critical for the homeostasis of the digestive and immune systems. Growing evidence indicates that dysregulation of the gut microbiome following allogeneic HSCT worsens aGVHD^{3,16,138}. Microbiome dysbiosis occurs following allo-HSCT due to broad-spectrum antibiotic use, conditioning therapy, and changes in host nutrition secondary to mucositis, nausea, and vomiting from the conditioning therapy¹³⁸. This dysbiosis can skew microbial populations and their metabolites. For instance, the short chain fatty acid microbial metabolite butyrate is reduced in murine models of aGVHD¹³⁹. Supplementation with butyrate or butyrate-producing bacteria ameliorated GI aGVHD by protecting intestinal epithelial cells from allo-T cell-mediated damage¹³⁹. Indole metabolites derived from microbial metabolism of tryptophan also protected mice from GI aGVHD via a type I IFN-dependent mechanism¹⁴⁰. In addition to microbial metabolites, prebiotics such as lactose, have also been shown to promote aGVHD by driving the outgrowth of aGVHD-associated *Enterococcus*¹⁴¹. Host factors secreted into the intestinal lumen, such as defensins and regenerating proteins, also mitigate acute GI GVHD by protecting the intestinal epithelium from bacterial translocation and decreasing crypt apoptosis^{3,142}. The Wnt agonist, R-spondin-1, augments this process by protecting intestinal stem cells from aGVHD and expanding paneth cells, which are then able to secrete more antimicrobial defensins^{143,144}.

In summary, the immunobiology of aGVHD is complex and involves essentially all aspects of the immune system. Allo-reactive T cells are central to aGVHD pathophysiology, and have been the main target of both treatment and prophylactic immune suppressive agents for aGVHD over the last 30 years. With greater mechanistic understanding of aGVHD immunobiology, additional therapeutic agents have been and continue to be developed. In the following sections, the immune suppressive strategies used to prevent and treat aGVHD (Figure 1) and additional immune dysregulation conditions associated with hematopoietic stem cell transplantation are described (Table 1).

GVHD PROPHYLAXIS

Calcineurin Inhibitors:

Primary GVHD prophylaxis revolves around the usage of CNIs, most prominently tacrolimus and cyclosporine^{145,146}. Calcineurin Inhibitors primarily prevent GVHD by blocking allogeneic T cell proliferation and IL-2 production¹⁴⁷⁻¹⁴⁹. They are associated with electrolyte abnormalities (hypomagnesemia notably with tacrolimus), nephrotoxicity, and hypertension. Close therapeutic drug monitoring to ensure target trough levels, can lessen many of these adverse risks. Gingival hyperplasia and hirsutism may additionally be seen with cyclosporine usage. Of note, tacrolimus and cyclosporine appear to also be associated with the serious post-transplant conditions of thrombotic microangiopathy (TMA) and posterior reversible encephalopathy syndrome (PRES). Given an increased risk of viral infections with their usage, Epstein-Barr virus associated post-transplant lymphoproliferative disease may be observed with CNIs. Despite the mentioned risks and necessity for close monitoring, CNIs are overall well tolerated and have been a cornerstone of aGVHD prophylaxis for decades.

Mycophenolate Mofetil:

Concurrent usage of CNIs and mycophenolate mofetil (MMF) in the prevention of GVHD continues to be explored. Most studies to date have evaluated MMF usage in non-myeloablative and reduced intensity conditioning regimens^{149,150}. By inhibiting the enzyme inosine monophosphate dehydrogenase (IMPDH), which lymphocytes particularly rely on for purine synthesis, mycophenolate acts by reducing lymphocyte proliferation^{146,151}. Infectious risks with MMF include JC virus-associated progressive multifocal leukoencephalopathy (PML), disseminated CMV or EBV, and reactivation of hepatitis B or C. Adverse drug reactions include peripheral edema, hypertension, hyperglycemia, nausea/vomiting, drug-related cytopenias, nephrotoxicity, and hepatic injury.

Methotrexate:

Low-dose intravenous methotrexate plus a CNI has also shown efficacy in the prevention of GVHD. Methotrexate impedes T cell activation by inhibiting dihydrofolate reductase resulting in impairment of lymphocyte DNA synthesis and repair. Dosing ranges from 10–15 mg/m² on days +1, +3, +6, and +11 following allogeneic transplantation^{145,152}. Leucovorin rescue is additionally administered in an effort to reduce toxicity to the kidneys, gastrointestinal tract and oral mucosa. However, such adverse effects are much less commonly seen than with anti-neoplastic high-dose methotrexate regimens. Leucovorin prevents these toxicities by displacing methotrexate from binding sites allowing cells to once again proceed with RNA and DNA synthesis.

Sirolimus:

Sirolimus acts via suppression of the mammalian target of rapamycin (mTOR) pathway leading to reduced IL-2 production and resultant blockage of T cell growth and proliferation. The agent has typically been used in combination with tacrolimus and methotrexate for the prevention of GVHD¹⁴⁹. Initial studies showed promise with the therapy, but later trials appeared to reveal a possible increased risk of veno-occlusive disease (VOD) and thrombotic microangiopathy (TMA) in those receiving sirolimus¹⁵³. Further studies are needed and are undergoing to fully understand the potential benefit of the agent in prevention of GVHD. Additional toxicities include hypertriglyceridemia, impaired wound healing, renal impairment, oral ulcers, and gastrointestinal complaints, including loose stools.

Anti-Thymocyte Globulin:

Polyclonal immunoglobulins targeting human T lymphocytes, e.g., anti-thymocyte globulin (ATG) therapy, may be beneficial in the prevention of acute and chronic GVHD, but a strong survival benefit has not been observed¹⁵⁴. When administered prior to donor cell infusion, they assist in reducing graft rejection, while the GVHD-related benefits are seen with delivery post-donor cell infusion. Adverse events to be aware of include risk for anaphylaxis, serum sickness with fever, and viral reactivation, including EBV and CMV.

Cyclophosphamide:

Post-transplant cyclophosphamide (PTCy) on days +3 and +4 has been found to reduce the incidence of acute and chronic GVHD through possible reduction of alloreactive T cells with

additional effects on regulatory T cells^{146,149,155,156}. This alkylating agent is now widely used and considered well tolerated even in the setting of additional calcineurin inhibition or MMF administration. The risk of hemorrhagic cystitis is reduced with aggressive intravenous hydration preceding, during and post-drug administration. Cardiotoxicity, myelosuppression, nephrotoxicity and nausea/vomiting may also be observed.

Experimental Therapies:

A potential promising new GVHD preventative agent is the histone deacetylase (HDAC) inhibitor, vorinostat. Lower doses of the drug appear to positively alter the balance of helper and regulatory T cells, reduce IL-6 and IL-12 production, and control dendritic cell activity¹⁵⁷. Initial trials demonstrated efficacy and safety when vorinostat was paired with MMF and tacrolimus¹⁵⁸. Side effects include hepatic toxicity, electrolyte abnormalities, QTc prolongation, mucositis and an elevated risk of bacterial infection.

An analogue of CTLA-4, Abatacept, inhibits T cell activation by blocking the co-stimulatory signal delivered between antigen presenting cells and T lymphocytes. Additional studies are needed, but early results, particularly with non-hematologic transplant indications, have shown a benefit^{159,160}. Infection risk is potentially less than other therapies, but remains present, especially when concurrent immunosuppressive therapy is used.

Alternative immunosuppressive/immune-modulatory mechanisms that have shown some benefit in the prevention of GVHD include CCR5 blockade via Marviroc¹⁶¹ and inhibition of dipeptidyl peptidase 4 (DPP-4) by Sitagliptin^{162,163}.

ACUTE GVHD TREATMENT

Corticosteroids:

Systemic corticosteroids (starting at 1–2 mg/kg/day) are the backbone of therapy for acute GVHD grade II or higher as well as for those suffering from moderate to severe chronic GVHD. Once symptoms stabilize or improve, corticosteroids are then weaned slowly as tolerated¹⁴⁶. Enteral corticosteroids, such as budesonide and beclomethasone, can be used in the setting of acute GI GVHD. The immunosuppressive effects of high-dose systemic and aberrantly absorbed local corticosteroids are numerous and include impaired antibody production, reduced T cell proliferation, increased proapoptotic lymphocyte activity, and alterations in leukocyte chemotaxis & anergy. Long-term exposure increases the risk of various opportunistic organisms, including DNA viruses (CMV, adenovirus, EBV and HHV-6), molds, and *Pneumocystis jiroveci*¹⁶⁴. Pneumocystis prophylaxis with pentamidine (inhaled or intravenous) or sulfamethoxazole-trimethoprim (following full hematologic count recovery) is thus imperative. Mold prophylaxis, such as micafungin, posaconazole, or voriconazole, may reduce the risk of serious disseminated fungemia. Hypertension, especially in the setting of additional calcineurin inhibitor usage, may necessitate treatment. Drug-induced hyperglycemia, metabolic syndrome, and hepatic cirrhosis can be seen. Finally, significant musculoskeletal side effects, including muscle atrophy and avascular necrosis, as well as psychological effects, such as irritability and insomnia, are observed with prolonged usage.

Ruxolitinib:

In those with steroid-resistant GVHD, there is growing evidence that the JAK1/2 inhibitor, ruxolitinib, is superior to additional second-line agents with good tolerance and excellent response rates¹⁶⁵. Down-regulation of the JAK-STAT pathway leads to reduced inflammatory cytokine production and subsequent inhibition of CD4 T cells, DCs, and NK cells. Following drug initiation, cytopenias (most prominently thrombocytopenia and anemia), transaminitis, and elevations in cholesterol/triglycerides may be seen. Infectious risks include viral reactivation, bacteremia, and fungal disease^{165,166}.

Tumor Necrosis Factor (TNF)-Inhibitors:

Tumor necrosis factor (TNF) inhibitors, such as infliximab and etanercept, reduce the response to TNF α , which is an inflammatory cytokine associated with aGVHD^{167,168}. Etanercept in addition to corticosteroid therapy may be effective for treating acute and chronic GVHD^{169,170}. Acute and delayed infusion reactions can be seen with delayed reactions manifesting similarly to serum sickness. TNF inhibition is associated with an increased risk of opportunistic fungal, bacterial, and mycobacterial infections. Hepatitis and zoster reactivations may additionally occur¹⁷¹.

Alemtuzumab:

Severe steroid-refractory aGVHD may necessitate treatment with the CD52 targeting agent, Alemtuzumab¹⁷². While often effective in improving aGVHD, alemtuzumab causes prolonged, profound lymphopenia that places the patient at an elevated risk of systemic bacterial and fungal infections, including aspergillosis. Worsening of underlying viral illnesses or viral reactivation may additionally be seen. Infusion-related reactions and thyroid disease are possible adverse reactions. Alemtuzumab has also been trialed as an GVHD preventative therapy prior to allogeneic transplantation. Prophylactic alemtuzumab reduced GVHD incidence and severity, but this was at the expense of increased rates of graft failure, delayed immune reconstitution, and increased rates of relapse. More favorable outcomes were observed when incorporated into non-malignant disease conditioning regimens¹⁴⁶.

Pentostatin:

The purine analog, pentostatin, may be effective for steroid-refractory aGVHD by inhibiting T cell proliferation¹⁷³. Just as with other immunosuppressive medications, pentostatin is associated with an increased risk for infection. With regard to cytopenias, pentostatin is primarily associated with lymphopenia. Renal, hepatic, and neurologic toxicities are possible, especially with high doses. Pulmonary dysfunction can be severe but occurs most often with concurrent use of fludarabine, thus dual therapy with these medications during conditioning is not recommended.

Interleukin-2 Receptor (CD25-alpha) Antibodies:

The cytokine interleukin-2 (IL-2) plays an important role in stimulating pro-inflammatory T lymphocyte pathways and thus blockage of the IL-2 receptor via basiliximab or daclizumab can be effective in the prevention of GVHD. Trials testing these agents for treatment of

acute GVHD were less promising^{146,174}. Overall, infectious complications were lower for these agents compared to other lymphocyte-targeting therapies, but an elevated risk of viral infections still appears to be present¹⁷¹.

Brentuximab:

Brentuximab, an anti-CD30 antibody, which is predominantly used in the treatment of classical Hodgkin lymphoma, showed a 24% partial response and 15% complete response rate in steroid-refractory acute GVHD¹⁷⁵. Neutropenia is often observed with frequent dosing (weekly). Acute pancreatitis, neuropathy, hyperglycemia, infusion-related reactions and hepatotoxicity may be seen. Despite targeting CD30-positive T lymphocytes, immunologic consequences (besides the mentioned neutropenia) appear to be less significant than those seen with other lymphocyte-targeting drugs¹⁶⁶.

Tocilizumab:

In those experiencing cytokine release syndrome as a result of chimeric antigen receptor T cell (CAR-T) therapy, the IL-6 receptor directed monoclonal antibody, Tocilizumab, can be extremely effective in reducing severe systemic inflammation¹⁷⁶. Early phase clinical studies showed promise in prevention of GVHD and treatment of acute and chronic GVHD^{177,178}. However, a recent phase III randomized double blind clinical trial reported nonsignificant trends toward reduced incidence of grade II-IV acute GVHD in recipients of HLA-matched unrelated donors, but no improvements in long-term survival¹⁷⁹. The drug appears to be associated with elevated rates of respiratory tract and cutaneous infections, in-addition to therapy-induced neutropenia and mycobacterium reactivation¹⁷¹. Non-immunologic/hematologic adverse drug events include increased serum cholesterol levels, transaminitis, infusion-related reactions, and hypertension.

Vedolizumab:

Vedolizumab is a monoclonal antibody that works by blocking $\alpha 4\beta 7$ integrin on T cells, thereby decreasing T cell trafficking to the gastrointestinal tract. Further efficacy and safety data regarding vedolizumab are needed, but the drug may be particularly helpful in those suffering from severe gastrointestinal aGVHD¹⁸⁰. Given its GI-specific mechanism of action, vedolizumab appears to not have a significant association with serious opportunistic infections; although, *Clostridium difficile* disease may be seen¹⁸¹.

Additional immunosuppression medications for non-GVHD indications:

Further immunosuppressive therapies may be used to treat additional post-HSCT complications, including immune-mediated cytopenias, thrombotic microangiopathy and idiopathic pneumonia syndrome.

Cytopenias that develop post-autologous or allogeneic HSCT due to varying types of immune dysregulation are associated with significant morbidity or mortality. All cell lines may be affected. Other than blood product transfusions, immunosuppressive agents may be utilized. Corticosteroids and intravenous immunoglobulins may be inadequate requiring the use of second-line agents, including drugs targeting T cell dysfunction and B cell driven antibody production¹⁸².

Thrombocytopenia and microangiopathic hemolytic anemia secondary to endothelial damage from excessive complement system activation can lead to post-transplant thrombotic microangiopathy. Treatment with blockade of the terminal complement component C5 via eculizumab has been shown to be efficacious¹⁸³.

As noted above, TNF-inhibition, may be used in those with steroid-refractory GVHD. Additionally, etanercept and infliximab have shown benefit in those with idiopathic pneumonia syndrome (IPS)^{184,185}. IPS typically presents within the first 100 days post-transplant as diffuse alveolar injury without apparent respiratory tract infection. Without treatment, the condition has a high mortality rate.

Rituximab:

The anti-CD20 monoclonal antibody, Rituximab, targets B lymphocytes and has been utilized for various hematopoietic stem cell transplantation related indications, including to treat immune-mediated post-transplant cytopenias¹⁸², and in an attempt to reduce chronic GVHD incidence by suppressing allogeneic donor B cell immunity¹⁸⁶. Given the propensity for EBV to target B lymphocytes, rituximab is also used to treat post-transplant EBV viremia/re-activation¹⁸⁷. Transient hypogammaglobulinemia may occur in patients following treatment. In addition, a small subset of patients may have persistent B cell lymphopenia resulting in prolonged hypogammaglobulinemia. Hepatitis B reactivation and progressive multifocal leukoencephalopathy have rarely been described¹⁷¹. Fever and infusion-related hypersensitivity may occur but can be prevented with pre-infusion acetaminophen, diphenhydramine, and/or corticosteroid administration.

Bortezomib:

The powerful proteasome inhibitor, Bortezomib, should be considered in treatment-resistant post-transplant immune-mediated cytopenias. By targeting plasma cells, the drug reduces production of antibodies directed against hematologic cells¹⁸². Those receiving bortezomib should be monitored closely for peripheral neuropathy, posterior reversible leukoencephalopathy syndrome, hepatotoxicity, cardiac dysfunction, herpes zoster reactivation, and gastrointestinal issues, including diarrhea and vomiting.

Eculizumab:

Inactivation of the terminal complement component CD5 by eculizumab can lead to a drastic improvement in patients suffering from post-transplant TMA¹⁸³. With complement suppression, the drug greatly increases the risk of meningococcal disease. Those receiving Eculizumab are thus recommended to receive immunizations targeting all serotypes of meningococcus prior to drug administration; although, this may not be feasible in the post-transplant setting. Routine antibacterial prophylaxis against encapsulated organisms is also administered to patients while receiving eculizumab¹⁷¹.

CONCLUSIONS

Immune suppression is used in allo-HSCT to prevent graft rejection, prevent GVHD, treat GVHD, and treat a number of other post-HSCT immune-related complications. Many of

these approaches are based on the rich knowledge of aGVHD immunobiology worked out in murine models and tested in clinical trials. The primary immune suppression strategy used for GVHD prophylaxis remains CNI-based, but newer promising approaches including PTCy, co-stimulatory receptor blockade, and HDAC inhibition may soon also become standard of care. The primary immune suppressive treatment for GVHD remains corticosteroids, but JAK inhibition with ruxolitinib is emerging as the preferred second-line therapy. As with all immune suppressive therapies, patients must be closely monitored for on- and off-target side effects. These side effects need to be balanced with the need to treat the underlying disorder. Much remains to be learned about the complex immunobiology of aGVHD, SR-aGVHD, and cGVHD. Advances in these areas will yield more effective and less toxic therapies in the future.

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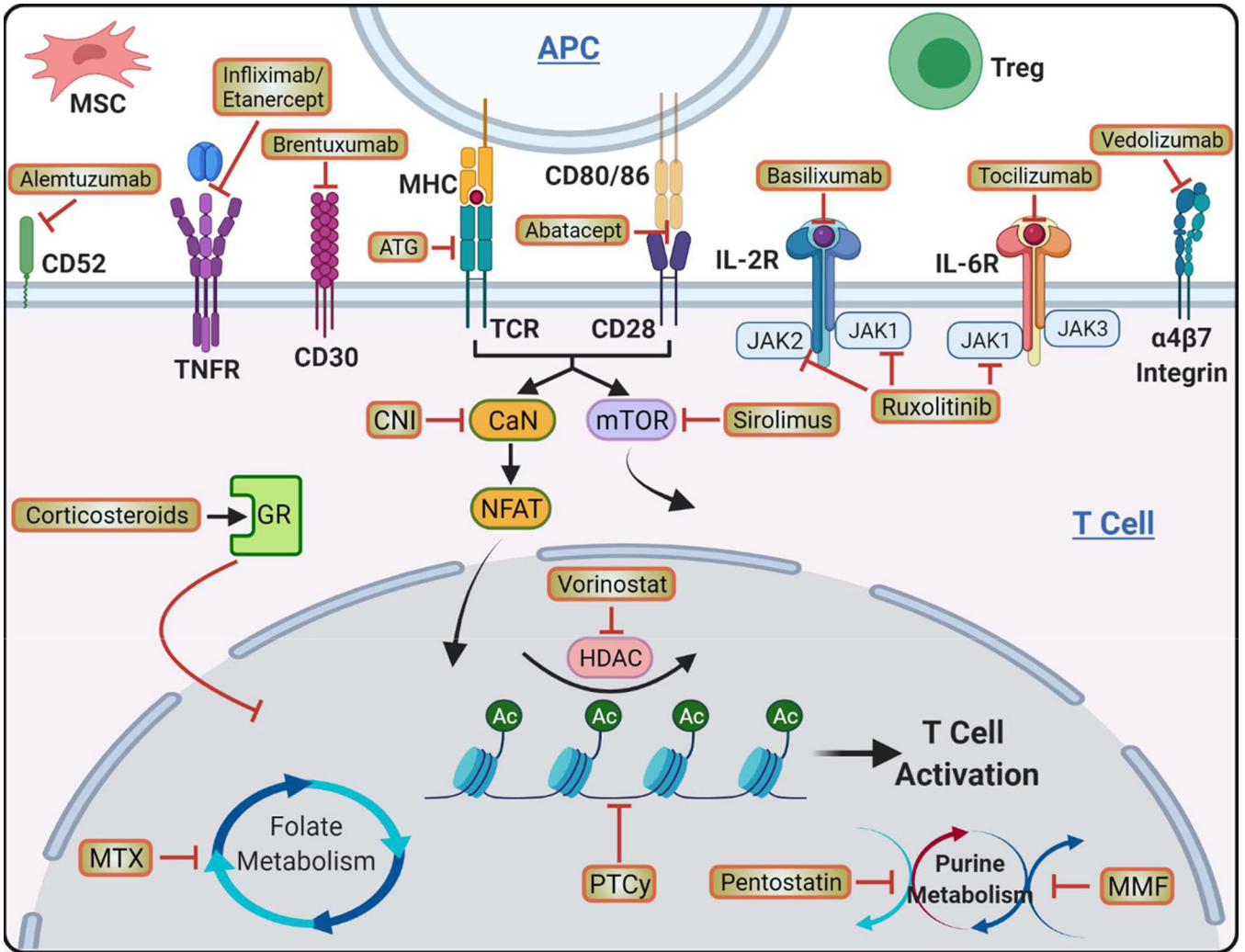


Figure 1: Immune suppressive therapies for aGVHD prevention and treatment.
 Ac: Acetylated; APC: Antigen presenting cell; ATG: Anti-thymocyte globulin; CaN: Calcineurin; CNI: Calcineurin inhibitor; GR: Glucocorticoid receptor; HDAC: Histone deacetylase; JAK: Janus kinase; MHC: Major histocompatibility complex; MMF: Mycophenolate mofetil; MSC: Mesenchymal stromal cell; mTOR: Mammalian target of rapamycin; MTX: Methotrexate; NFAT: Nuclear factor of activated T cells; PTCy: Post-transplantation cyclophosphamide; Treg: Regulatory helper T cell. This image was made using BioRender.

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Table 1: Immune suppressive therapies for various hematopoietic stem cell transplantation indications.

Drug	Mechanism of Action	Primary Indication	Notable Adverse Effects
Tacrolimus/Cyclosporine (CSA)	Calcineurin Inhibition	GVHD prophylaxis	Hypomagnesemia (tacrolimus), renal dysfunction, hypertension, PRES, TMA, gingival hyperplasia (CSA), hirsutism (CSA), viral infections
Mycophenolate Mofetil	Inhibiting the enzyme inosine monophosphate dehydrogenase	GVHD prophylaxis	JC virus-associated progressive multifocal leukoencephalopathy, viral infections, hypertension, peripheral edema, hyperglycemia, cytopenias, nephrotoxicity, liver injury
Methotrexate	Dihydrofolate reductase suppression	GVHD prophylaxis	Nephrotoxicity, cytopenias, gastrointestinal issues, oral mucositis; leucovorin rescue imperative
Sirolimus	Mammalian target of rapamycin (mTOR) inhibition	GVHD prophylaxis	Hypertriglyceridemia, impaired wound healing, renal impairment, oral ulcers, gastrointestinal complaints, increased risk of infections
Anti-Thymocyte Globulin	T lymphocyte destruction	GVHD prophylaxis	Serum sickness, infusion reaction, viral reactivation
Cyclophosphamide	Alkylating agent resulting in T cell modifications	GVHD prophylaxis	Cardiotoxicity, myelosuppression, nephrotoxicity, hemorrhagic cystitis, nausea/vomiting
Vorinostat	Histone deacetylase inhibitor	GVHD prophylaxis	Hepatic injury, electrolyte abnormalities, risk for bacterial infections, cardiac arrhythmias (QTc prolongation), mucositis
Abatacept	CTLA-4 analogue	GVHD prophylaxis	Viral infections, hypersensitivity reaction, headaches, nausea
Maraviroc	CCR5 blockade	GVHD prophylaxis	Dizziness, hepatotoxicity, risk of infections, hypersensitivity, skin rash, vomiting, fever
Sitagliptin	Inhibition of dipeptidyl peptidase 4 (DPP-4)	GVHD prophylaxis	Hyperglycemia, rash, acute pancreatitis, liver toxicity, nephrotoxicity
Prednisone/ Methylprednisolone, Budesonide/Beclomethasone	Corticosteroids (systemic/enteral)	GVHD treatment	Opportunistic infections including pneumocystis, hyperglycemia, hypertension, hepatic cirrhosis, avascular necrosis
Ruxolitinib	JAK1/2 inhibition	GVHD treatment	Cytopenias (thrombocytopenia, anemia), hepatic toxicity, increased infectious risk, elevated serum cholesterol, hypertriglyceridemia
Infliximab, Etanercept	Tumor necrosis factor inhibitors	GVHD treatment, treatment of IPS	Infusion reactions (acute & delayed), opportunistic infections, hepatic toxicity, anemia, abdominal pain, rash
Alemtuzumab	anti-CD52	GVHD treatment	Prolonged significant lymphopenia, high infection risk, infusion reaction, thyroid disease, cytopenias, autoimmune hepatitis, skin rash, fever
Pentostatin	Purine analogue	GVHD treatment	Infections, lymphopenia, pulmonary dysfunction, gastrointestinal complaints, central nervous system toxicity, rash, hepatitis, fatigue, fever
Basiliximab, Daclizumab	Interleukin-2 Receptor (CD25-alpha) antibodies	GVHD prophylaxis/treatment	Viral infections, hypertension, hyperglycemia, electrolyte abnormalities, hepatic toxicity, rash
Brentuximab	anti-CD30	GVHD treatment	Acute pancreatitis, neuropathy, hyperglycemia, infusion-related reactions, neutropenia, hepatotoxicity
Tocilizumab	Interleukin-6 receptor monoclonal antibody	GVHD treatment	Respiratory tract & cutaneous infections, neutropenia, mycobacterium reactivation, increased serum cholesterol, transaminitis, infusion-related reactions, hypertension

Drug	Mechanism of Action	Primary Indication	Notable Adverse Effects
Vedolizumab	Inhibition of mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and alpha4beta7 integrin interaction	Gastrointestinal GVHD treatment	<i>Clostridium difficile</i> disease, infusion-related reactions, headache, arthralgias
Rituximab	anti-CD20	Post-transplant immune-mediated cytopenias, EBV viremia, GVHD prevention	Hypogammaglobulinemia, B cell lymphopenia, infusion-related hypersensitivity, fever, hepatitis B reactivation
Bortezomib	Proteasome inhibitor	Post-transplant immune-mediated cytopenias	Peripheral neuropathy, posterior reversible leukoencephalopathy syndrome, hepatotoxicity, cardiac dysfunction, herpes zoster reactivation, gastrointestinal issues
Eculizumab	Inactivation of terminal complement component C5	Treatment of TMA	Significant risk for meningococcal disease & encapsulated organisms (antimicrobial prophylaxis required), hypertension/tachycardia, headache, hypokalemia, rash, diarrhea/nausea/vomiting, anemia/leukopenia, fever, renal insufficiency

GVHD: Graft-versus-host disease; PRES: Posterior reversible encephalopathy syndrome; TMA: Thrombotic microangiopathy; CTLA-4: Cytotoxic T-lymphocyte-associated antigen-4; CCR5: C-C Chemokine Receptor Type 5; IPS: Idiopathic pneumonia syndrome.