Immune Suppression in Allogeneic Hematopoietic Stem Cell Transplantation

Thomas F. Michniacki, Sung Won Choi, and Daniel C. Peltier

Contents

1 Introduction 210
2 Clinical Features of aGVHD 211
3 Influence of Donor Graft, MHC Matching, and Conditioning on aGVHD 213
4 Chronic GVHD 215
5 Immunobiology of aGVHD 215
5.1 Tissue Injury and Inflammation from Pre-transplant Conditioning (aGVHD Triggers and Sensors) 216
5.2 Stimulation, Differentiation, and Proliferation of Effector T Cells (aGVHD Mediators) 217
5.3 Tissue Damage by Effectors and Inflammatory Cytokines (aGVHD Effectors and Amplifiers) 219
5.4 Tissue Repair and Anti-inflammatory Mechanisms (aGVHD Modulators) 219
6 GVHD Prophylaxis 227
6.1 Calcineurin Inhibitors 227
6.2 Mycophenolate Mofetil 228
6.3 Methotrexate 228
6.4 Sirolimus 228
6.5 Anti-Thymocyte Globulin 229
6.6 Cyclophosphamide 229
6.7 Experimental Therapies 229
7 Acute GVHD Treatment 230
7.1 Corticosteroids 230

T. F. Michniacki
Division of Hematology/Oncology, Department of Pediatrics, Blood and Marrow Transplantation Program, University of Michigan, Ann Arbor, MI, USA

S. W. Choi (✉) · D. C. Peltier (✉)
Division of Hematology/Oncology, Department of Pediatrics, Blood and Marrow Transplantation Program, University of Michigan, Ann Arbor, MI, USA

University of Michigan Rogel Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI, USA
e-mail: sungchoi@med.umich.edu; peltierd@med.umich.edu

H. J. Eisen (ed.), *Pharmacology of Immunosuppression,*
Handbook of Experimental Pharmacology 272, https://doi.org/10.1007/164_2021_544

7.2 Ruxolitinib 230
7.3 Tumor Necrosis Factor (TNF)-Inhibitors 231
7.4 Alemtuzumab 231
7.5 Pentostatin 231
7.6 Interleukin-2 Receptor (CD25-Alpha) Antibodies 232
7.7 Brentuximab 232
7.8 Tocilizumab 232
7.9 Vedolizumab 232
7.10 Additional Immunosuppression Medications for Non-GVHD Indications 233
7.11 Rituximab 233
7.12 Bortezomib 234
7.13 Eculizumab 234
8 Conclusions 234
References 235

Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative treatment for high-risk hematologic disorders. There are multiple immune-mediated complications following allo-HSCT that are prevented and/or treated by immunosuppressive agents. Principal among these immune-mediated complications is acute graft-versus-host disease (aGVHD), which occurs when the new donor immune system targets host tissue antigens. The immunobiology of aGVHD is complex and involves all aspects of the immune system. Due to the risk of aGVHD, immunosuppressive aGVHD prophylaxis is required for nearly all allogeneic HSCT recipients. Despite prophylaxis, aGVHD remains a major cause of nonrelapse mortality. Here, we discuss the clinical features of aGVHD, the immunobiology of aGVHD, the immunosuppressive therapies used to prevent and treat aGVHD, how to mitigate the side effects of these immunosuppressive therapies, and what additional immune-mediated post-allo-HSCT complications are also treated with immunosuppression.

Keywords

Acute graft-versus-host disease · Allogeneic hematopoietic stem cell transplantation · Immune suppression

1 Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative modality for high-risk malignancies, hematologic disorders, immunologic disorders, and metabolic disorders (Hołowiecki 2008). Fundamentally, HSCT results in a 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 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 allogenic 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) tract (Ferrara et al. 2009). 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 a major life-threatening complication of allogeneic HSCT (Ferrara et al. 2009). 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.

2 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 affected (Zeiser and Blazar 2017a). Acute GVHD typically manifests within the first 100 days after transplantation; however, it can occur later (Zeiser and Blazar 2017a). 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 (Zeiser and Blazar 2017a; Jagasia et al. 2012; Flowers et al. 2011; Hahn et al. 2008).

The skin is typically the first organ affected by aGVHD (Ferrara et al. 2009). Signs of skin aGVHD include an erythematous maculo-papular rash that can

advance to blisters and ulceration (Ferrara et al. 2009; Zeiser and Blazar 2017a). Early skin aGVHD has a predilection for the palms, soles, ears, neck, and dorsal surfaces of the extremities and malar regions (Ferrara et al. 2009; Zeiser and Blazar 2017a). 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 dermis (Zeiser and Blazar 2017a). 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 (Haimes et al. 2019; Zhou et al. 2000). Upper GI aGVHD typically manifests with nausea, weight loss, and anorexia (Ferrara et al. 2009; Zeiser and Blazar 2017a). Patchy ulcerations and flattening of surface epithelium are typically seen on histopathology (Zeiser and Blazar 2017a). Lower GI aGVHD manifests as watery and/or bloody diarrhea with or without crampy abdominal pain (Ferrara et al. 2009; Zeiser and Blazar 2017a). Apoptotic bodies and abscesses in the epithelial crypts are diagnostic on histopathology of endoscopic biopsies (Ferrara et al. 2009; Zeiser and Blazar 2017a). Liver aGVHD clinically manifests with elevated total bilirubin with or without jaundice (Ferrara et al. 2009; Zeiser and Blazar 2017a). Pathology is notable for lymphocytic infiltration near port veins and bile ducts with bile duct loss occurring in advanced lesions (Ferrara et al. 2009; Zeiser and Blazar 2017a).

The severity of aGVHD is staged within each of the primary target organs: skin, liver, and gut (Glucksberg et al. 1974; Przepiorka et al. 1995). These stages are then combined into an overall grade (Glucksberg et al. 1974; Przepiorka et al. 1995). 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, <2 mg/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 ≥50 kg 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, >1,000 mL/day or >60 mL/kg; stage 3, >1,500 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 (Przepiorka et al. 1995; MacMillan et al. 2020). 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% (Zeiser and Blazar 2017a). 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 (MacMillan et al. 2020; Levine et al. 2015; Hartwell et al. 2017; Major-Monfried et al. 2018; Gergoudis et al. 2020).

3 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 (Zeiser and Blazar 2017a; Hill et al. 2021). 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 expression (Summers et al. 2020). 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 responses (Summers et al. 2020). 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 mismatch (Zeiser and Blazar 2017a). 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 prophylaxis (Ferrara et al. 2009).

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 DR3/4/5 (Dehn et al. 2019). 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 unavailable (Dehn et al. 2019). 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 (Jagasia et al. 2012; Flowers et al. 2011; Loiseau et al. 2007). 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. (Dehn et al. 2019; Eapen et al. 2011; Eapen et al. 2017) 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 transplantation (McCurdy and Luznik 2019).

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 blood (Ballen et al. 2013).

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 (Zeiser and Blazar 2017a; Flowers et al. 2011; Gooptu and Koreth 2020). 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 αβ 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 cells (Gooptu and Koreth 2020). 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 grafts (Gooptu and Koreth 2020). T cells are also critical for engraftment and immune recovery; therefore, T cell-depleted grafts often have higher rates of graft failure and infections (Gooptu and Koreth 2020).

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 (Zeiser and Blazar 2017a; Jagasia et al. 2012). Full intensity, myeloablative conditioning regimens are typically associated with a greater risk of aGVHD (Jagasia et al. 2012; Nakasone et al. 2015). 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 cells (Zeiser and Blazar 2017a).

4 Chronic GVHD

Chronic GVHD (cGVHD) is a significant risk factor for nonrelapse mortality in patients two years or greater post allo-HSCT (Zeiser and Blazar 2017b). It is classically defined as occurring >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) (Ferrara et al. 2009). Virtually every organ system can be affected by cGVHD, which resembles an "autoimmune syndrome" (Zeiser and Blazar 2017b; Saidu et al. 2020). 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 (Ferrara et al. 2009; Zeiser and Blazar 2017b; Saidu et al. 2020). Diagnosis, staging, and response grading of cGVHD are based on the National Institutes of Health Consensus Criteria (Lee et al. 2015; Jagasia et al. 2015). 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 recipients (Flowers et al. 2011).

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 (Hill et al. 2021; Zeiser and Blazar 2017b). A more detailed description of cGVHD immunobiology and management with immune suppression is 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 (Zeiser and Blazar 2017b; Saidu et al. 2020; Grube et al. 2016). Therefore, we will point out those immunosuppressive agents used for both acute and chronic GVHD.

5 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 damage (Antin and Ferrara 1992). Similar to an immune response to a pathogen, the immunobiology of aGVHD consists of triggers, sensors, mediators, effectors, amplifiers, and modulators (Reddy 2012). 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.

5.1 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) (Zeiser and Blazar 2017a; Wilhelm et al. 2010; Jankovic et al. 2013). 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) (Zeiser and Blazar 2017a). Alarmin molecules (IL-1α, 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 tissues (Hill et al. 2021). Ligand-bound PRRs and alarmin receptors initiate signaling pathways (e.g., NF-κB) that activate cytokine (e.g., TNFα, IL-1β, IL-6, IL-33, IL-12, IL-23, type I IFNs) and chemokine (e.g., CCL5) production (Zeiser and Blazar 2017a; Hill et al. 2021; Hill and Koyama 2020). 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 (Zeiser and Blazar 2017a; Hill et al. 2021; Hill and Koyama 2020).

APCs are the main sensors of aGVHD. The inflammatory environment created by the conditioning regimen activates host APCs (e.g., dendritic cells and macrophages) (Zeiser and Blazar 2017a; Hill et al. 2021). Activated APCs increase allo-antigen presentation, upregulate co-stimulatory molecules, and secrete inflammatory cytokines (Zeiser and Blazar 2017a; Hill et al. 2021). 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 (Hill et al. 2021; Koyama et al. 2015). Allogeneic antigens are also presented by non-hematopoietic host tissues (Koyama et al. 2011; Koyama et al. 2019; Toubai et al. 2012). 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 aGVHD (Koyama et al. 2019).

5.2 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 proliferation (Hill et al. 2021). In murine models, naïve ($CD62L^+$ $CD45RA^+$ $CCR7^+$) T cells (i.e., antigen-inexperienced) are far more likely to cause aGVHD than memory T-cells (Hill et al. 2021; Chen et al. 2007). However, human recipients of naïve T cell-depleted grafts still develop aGVHD (Gooptu and Koreth 2020; Bleakley et al. 2015). 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 metabolism (Zeiser and Blazar 2017a). Similarly, the Notch ligand DLL4 expressed on non-hematopoietic stromal cells also promotes allogeneic T cell-driven aGVHD (Hill and Koyama 2020; Chung et al. 2017).

Signal transduction downstream of the T cell receptor and co-stimulatory receptors starts with receptor-proximal phosphorylation of signaling molecules (Gaud et al. 2018; Huse 2009). This then promotes the activation of phospholipase C which hydrolyzes phosphatidylinositol bisphosphate (PIP_2) to yield diacylglycerol (DAG) and inositol trisphosphate (IP_3). DAG recruits a number of downstream signaling molecules including protein kinase C-θ (PKCθ) that results in the activation of the mitogen-activated protein kinase (MAPK) cascade and culminates in the activation of the transcription factor AP-1. PKCθ also induces a signaling pathway leading to the activation of the transcription factor NF-κB. Meanwhile, IP_3 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-κB that induce the expression of a number of

genes that promote the activation and proliferation of T cells including IL-2 (Gaud et al. 2018; Huse 2009).

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 (Hill et al. 2021; Fu et al. 2014). The inflammatory cytokine milieu present post-HSCT generally polarizes CD4 helper and CD8 cytotoxic T cells toward the inflammatory Th1/Th17 and Tc1/Tc17 subsets, respectively (Hill et al. 2021; Fu et al. 2014). 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 TGFβ. IL-6 also inhibits the induction of Tregs. In contrast to IL-12 and IFNγ, IL-4 levels, which support Th2/Tc 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 (Hill et al. 2021; Fu et al. 2014). 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 TGFβ) ameliorate aGVHD (Hill et al. 2021; Fu et al. 2014). 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 cells (Takashima et al. 2019). 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 irradiation (Welniak et al. 2000). This discrepancy was shown to be due in part to IFN-γ's ability to protect against Th2-mediated lung damage (Hill et al. 2021; Fu et al. 2014). Nevertheless, donor T cells deficient for the Th1-specific transcription factor, T-bet, caused less severe aGVHD (Fu et al. 2015). 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 blocked (Yi et al. 2009).

Helper T cell subsets differentially express chemokine receptors that govern their trafficking to target tissues (Fu et al. 2014). Th1 cells express CCR5 and CXCR3, which aids their trafficking to the gut and liver, respectively (Fu et al. 2014). Th17 cells express CCR6 promoting trafficking to the skin, and Th2 cells express CCR4 allowing them to traffic to the lungs (Fu et al. 2014). 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 active donor T cells and imprint them with gut-homing expression of α4β7 integrin (Koyama et al. 2015). This leads to the migration of allogeneic T cells into the GI tract where they cause fulminant disease (Koyama et al. 2015).

5.3 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-1β, TNFα, IFN-γ), and reactive oxygen species (ROS) (Zeiser and Blazar 2017a; Hill et al. 2021). 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 (Zeiser and Blazar 2017a; Hill et al. 2021).

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 (Divito et al. 2020; Strobl et al. 2020). 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 (Du and Cao 2018; Shlomchik 2007). 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 cells (Du and Cao 2018). 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 ß (LTß)/LIGHT pathway (Reddy 2012).

Inflammatory pathways do not require cell–cell contact to kill target cells. Instead, target cell damage is caused by cytotoxic cytokines (TNFα and IFNγ) and ROS released by allogeneic T cells and inflammatory monocytes, respectively (Zeiser and Blazar 2017a; Schwab et al. 2014). 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 (Hill et al. 2021; Du and Cao 2018). Therefore, the utility of therapeutically targeting aGVHD effector mechanisms is uncertain.

5.4 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 express not only 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 (Zeiser and Blazar 2017a; Hill et al. 2021). In addition, many cytokines secreted by activated T

cells (e.g., IFNy, IL-12, IL-22, IL-10, TGFβ, and IL-2) have both pro- and anti-aGVHD affects depending on the context and model system (Zeiser and Blazar 2017a; Hill et al. 2021; Hill and Koyama 2020). 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 aGVHD (Yu et al. 2019). 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 models (Sato et al. 2003). 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 (Li et al. 2020; Choi and Reddy 2011).

Similar to DCs, macrophages are an APC that also regulates aGVHD in complex ways (Hong et al. 2020). 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 (Nishiwaki et al. 2014; Cheng et al. 2015). However, other studies have shown that host macrophages attenuate aGVHD in murine models (Nieves et al. 2017; Hashimoto et al. 2011). 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 patients (Holtan et al. 2019). By contrast, G-CSF-mobilized HSCT grafts with higher levels of M2 macrophages were associated with less subsequent aGVHD (Wen et al. 2019).

A subset of monocytic and granulocytic myeloid cells, termed myeloid derived suppressor cells (MDSC), are highly immune suppressive (Zeiser and Blazar 2017a; Voermans and Hazenberg 2020). Adoptively transferred MDSCs promoted tolerogenic Th2 and Treg responses thereby suppressing murine aGVHD (Voermans and Hazenberg 2020; Ghansah et al. 2004; Vendramin et al. 2014; Fan et al. 2017; Wang et al. 2019; Highfill et al. 2010; Zhang et al. 2019). However, MDSCs can lose their suppressor function by inflammasome activation when in pro-inflammatory environments (Koehn et al. 2015; Koehn et al. 2019). 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. (Voermans and Hazenberg 2020; Cheung et al. 2020) 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 (Voermans and Hazenberg 2020; Cheung

et al. 2020). A number of small heterogeneous studies showed variable responses of steroid-refractory aGVHD (SR-aGVHD) to MSC therapy (Voermans and Hazenberg 2020; Cheung et al. 2020). One multicenter, randomized controlled trial did not meet its primary endpoint of improved durable complete remission (Kebriaei et al. 2020). 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 study (Kurtzberg et al. 2020). Importantly, MSCs are safe and well tolerated (Voermans and Hazenberg 2020; Cheung et al. 2020). 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 aGVHD (Hill et al. 2021). $CD4^+$ $FOXP3^+$ $CD25^+$ Tregs arise directly following thymic maturation or are induced in the periphery from CD4 T cells (Mancusi et al. 2019). Acute GVHD is associated with deficient Treg reconstitution and reduced Treg function in pre-clinical and clinical studies (Mancusi et al. 2019; Elias and Rudensky 2019). 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 aGVHD (Mancusi et al. 2019; Elias and Rudensky 2019; Taylor et al. 2002; Nguyen et al. 2007). In early-phase clinical trials, adoptive transfer of Tregs appears safe and effective for aGVHD prevention without causing greater leukemia relapse (Meyer et al. 2019; Di Ianni et al. 2011; Martelli et al. 2014; Brunstein et al. 2016). The ability of Tregs to treat clinic aGVHD remains to be determined (Trzonkowski et al. 2009). 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 (Hill et al. 2021; Mancusi et al. 2019; Elias and Rudensky 2019). 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 (Koreth et al. 2011; Matsuoka et al. 2013). Calcineurin inhibitors (CNIs), which are commonly used for aGVHD prophylaxis, inhibit IL-2 production and may hinder Treg recovery post-HSCT (Zeiser et al. 2006). 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 vivo (Zeiser et al. 2006; Whitehouse et al. 2017; Furlan et al. 2020).

Alpha-1-antitrypsin (AAT) is a serine protease inhibitor produced by the liver and is lost through the GI tract especially with GI aGVHD (Rodriguez-Otero et al. 2012). In murine models, AAT administration was effective at preventing and treating aGVHD (Tawara et al. 2012; Marcondes et al. 2014). The anti-aGVHD mechanism of AAT is not clear, but may involve promoting Treg recovery and altering inflammatory cytokine production (Tawara et al. 2012; Marcondes et al. 2014; Magenau

et al. 2018). A phase 2 clinical trial showed promising responses in steroid-refractory acute GVHD (Magenau et al. 2018).

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 (Kebriaei et al. 2020; Shimabukuro-Vornhagen et al. 2009; Schultz et al. 1995; Kamble et al. 2006; Ratanatharathorn et al. 2009; Khouri et al. 2008; Shimoni et al. 2003; Christopeit et al. 2009). Human HSCT grafts with high numbers of B lymphocytes correlated with an increased incidence of aGVHD (Iori et al. 2008). 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-10 (Weber et al. 2014). Co-transfer of regulatory B cells also attenuated murine aGVHD (Hill et al. 2021; Hu et al. 2017). In humans, grafts with a high content of B cell progenitors are associated with less aGVHD (Michonneau et al. 2009). 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 antitumor and antimicrobial properties. They are the first donor lymphoid cell to recover post-HSCT (Simonetta et al. 2017). 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 (Simonetta et al. 2017; Acevedo et al. 1991; Roy et al. 1993; Guillén et al. 1986). However, subsequent studies suggested that NK cells regulated alloimmune T cells via direct cytotoxic mechanisms resulting in less aGVHD (Simonetta et al. 2017; Murphy et al. 1992; Ruggeri et al. 2002; Olson et al. 2010). 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 (Simonetta et al. 2017; Xun et al. 1995; Xun et al. 1993; Cooley et al. 2005; Shah et al. 2015). Nonetheless, most clinical studies of adoptively transferred NK cells did not increase the incidence of aGVHD (Simonetta et al. 2017; Passweg et al. 2004; Choi et al. 2014a; Jaiswal et al. 2017).

Invariant natural killer cells (iNKT) are $CD3^+$, $CD4^+$, or $CD4^-$ cells that express NK cell markers and an invariant αβ TCR. Invariant NKT cells respond to lipid molecules presented by the non-polymorphic MHC-I-like CD1d molecule (Voermans and Hazenberg 2020). When activated, these cells promote tolerance by secreting IL-4 and IL-13 (Voermans and Hazenberg 2020; Andrlová et al. 2020). Human grafts with high iNKT cells numbers are associated with a lower incidence of aGVHD (Chaidos et al. 2012). In mice, iNKT cells protected against aGVHD (Voermans and Hazenberg 2020; Andrlová et al. 2020; Schneidawind et al. 2014; Schneidawind et al. 2015). In humans, the iNKT agonist RGI-2001 decreased the incidence of aGVHD (Chen et al. 2017a). 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, MR1 (Andrlová et al. 2020). Mouse studies show that recipient MAIT cells reduce GI aGVHD by promoting intestinal barrier function in an IL-17-dependent manner (Varelias et al. 2018). The association of MAIT cell reconstitution and clinical aGVHD is variable and requires further study (Voermans and Hazenberg 2020; Bhattacharyya et al. 2018; Ben Youssef et al. 2018; Kawaguchi et al. 2018).

Gamma-delta (γ/δ)T cells are unconventional T cells activated by phosphoantigens (Andrlová et al. 2020). Their role in aGVHD is uncertain. Murine models demonstrated that both host and recipient γ/δ T cells exacerbated aGVHD (Blazar et al. 1996; Maeda et al. 2005). However, the clinical evidence for human γ/δ T cells exacerbating aGVHD is variable (Andrlová et al. 2020). 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 (Locatelli et al. 2017; de Witte et al. 2021).

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 (Voermans and Hazenberg 2020; Shao et al. 2019). Secretion of IL-22 by recipient ILC3 cells protected intestinal stem cells from allogeneic T cell-mediated damage and ameliorated aGVHD in mice (Hanash et al. 2012). Transfer of donor ILC2 cells treated established murine aGVHD by activating anti-inflammatory MDSCs in an IL-13-dependent manner (Bruce et al. 2017). Delayed ILC reconstitution in humans has also been associated with a higher risk for aGVHD (Munneke et al. 2014). 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 (Zeiser and Blazar 2017a; Hill et al. 2021; Rafei and Jenq 2020). 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 therapy (Rafei and Jenq 2020). 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 aGVHD (Mathewson et al. 2016). Supplementation with butyrate or butyrate-producing bacteria ameliorated GI aGVHD by protecting intestinal epithelial cells from allo-T cell-mediated damage (Mathewson et al. 2016). Indole metabolites derived from microbial metabolism of tryptophan also protected mice from GI aGVHD via a type I IFN-dependent mechanism (Swimm et al. 2018). In addition to microbial metabolites, prebiotics such as lactose have also been shown to promote aGVHD by driving the outgrowth of aGVHD-associated *Enterococcus (*Stein-Thoeringer et al. 2019*)*. 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

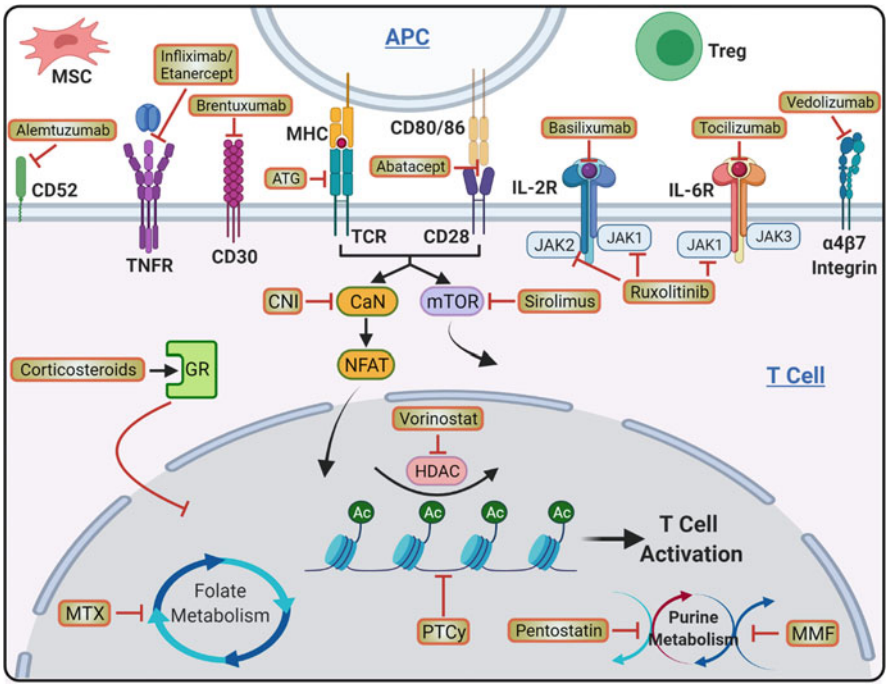

Fig. 1 Immune suppressive therapies for aGVHD prevention and treatment. *Ac* Acetylated, *APC* Antigen presenting cell, *ATG* Anti-thymocyte globulin, *CaN* Calcineurin, *CNI* Calcineurin inhibitor, *GR* Glucocorticoid receptor, *HDAC* Histone deacetylase, *JAK* Janus kinase, *MHC* Major histocompatibility 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

(Zeiser and Blazar 2017a; Zhao et al. 2018). 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 (Hayase et al. 2017; Takashima et al. 2011).

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 (Fig. 1) and additional immune dysregulation conditions associated with hematopoietic stem cell transplantation are described (Table 1).

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 analog	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	Hypoglycemia, rash, acute pancreatitis, liver toxicity, nephrotoxicity

(continued)

Table 1 (continued)

Drug	Mechanism of action	Primary indication	Notable adverse effects
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 and 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 analog	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 and cutaneous infections, neutropenia, mycobacterium reactivation, increased serum cholesterol, transaminitis, infusion-related reactions, hypertension

(continued)

Table 1 (continued)

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	*C. difficile* 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 CD5	Treatment of TMA	Significant risk for meningococcal disease and 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

6 GVHD Prophylaxis

6.1 Calcineurin Inhibitors

Primary GVHD prophylaxis revolves around the usage of CNIs, most prominently tacrolimus and cyclosporine (Choi et al. 2010; Gatza et al. 2020). Calcineurin inhibitors primarily prevent GVHD by blocking allogeneic T cell proliferation and IL-2 production (Chinen and Shearer 2010; Heidt et al. 2010; Choi and Reddy 2014). 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.

6.2 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 (Choi and Reddy 2014; Ruutu et al. 2014). By inhibiting the enzyme inosine monophosphate dehydrogenase (IMPDH), which lymphocytes particularly rely on for purine synthesis, mycophenolate acts by reducing lymphocyte proliferation (Gatza et al. 2020; Cuny et al. 2017). 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.

6.3 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/m^2 on days +1, +3, +6, and + 11 following allogeneic transplantation (Choi et al. 2010; Nash et al. 1996). 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.

6.4 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 GVHD (Choi and Reddy 2014). 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 sirolimus (Pulsipher et al. 2014). 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.

6.5 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 observed (Arai et al. 2017). 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.

6.6 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 allo-reactive T cells with additional effects on regulatory T cells (Gatza et al. 2020; Choi and Reddy 2014; Wachsmuth et al. 2019; Kanakry et al. 2013). 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.

6.7 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 activity (Holtan and Weisdorf 2017). Initial trials demonstrated efficacy and safety when vorinostat was paired with MMF and tacrolimus (Choi et al. 2014b). Side effects include hepatic toxicity, electrolyte abnormalities, QTc prolongation, mucositis, and an elevated risk of bacterial infection.

An analog 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 (Khandelwal et al. 2021; Ngwube et al. 2020). 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 Marviroc (Moy et al. 2017) and inhibition of dipeptidyl peptidase 4 (DPP-4) by Sitagliptin (Farag et al. 2021; Martin 2021).

7 Acute GVHD Treatment

7.1 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 tolerated (Gatza et al. 2020). 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 (*Youssef et al. 2016*)*. 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.

7.2 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 rates (Zeiser et al. 2020). 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 (Zeiser et al. 2020; Maschmeyer et al. 2019).

7.3 Tumor Necrosis Factor (TNF)-Inhibitors

Tumor necrosis factor (TNF) inhibitors, such as infliximab and etanercept, reduce the response to TNFα, which is an inflammatory cytokine associated with aGVHD (Salomon et al. 2018; Holler et al. 1990). Etanercept in addition to corticosteroid therapy may be effective for treating acute and chronic GVHD (Levine et al. 2008; Chiang et al. 2002). 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 occur (Henrickson et al. 2016).

7.4 Alemtuzumab

Severe steroid-refractory aGVHD may necessitate treatment with the CD52 targeting agent, Alemtuzumab (Schnitzler et al. 2009). 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 a 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 regimens (Gatza et al. 2020).

7.5 Pentostatin

The purine analog, pentostatin, may be effective for steroid-refractory aGVHD by inhibiting T cell proliferation (Bolaños-Meade et al. 2005). 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.

7.6 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 (Gatza et al. 2020; Ross and Cantrell 2018). 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 present (Henrickson et al. 2016).

7.7 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 GVHD (Chen et al. 2017b). 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 drugs (Maschmeyer et al. 2019).

7.8 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 inflammation (Si and Teachey 2020). Early phase clinical studies showed promise in prevention of GVHD and treatment of acute and chronic GVHD (Drobyski et al. 2011; Kennedy et al. 2014). 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 survival (Kennedy et al. 2021). The drug appears to be associated with elevated rates of respiratory tract and cutaneous infections, in addition to therapy-induced neutropenia and mycobacterium reactivation (Henrickson et al. 2016). Non-immunologic/hematologic adverse drug events include increased serum cholesterol levels, transaminitis, infusion-related reactions, and hypertension.

7.9 Vedolizumab

Vedolizomab is a monoclonal antibody that works by blocking α4β7 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 aGVHD (Fløisand et al. 2019). 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 seen (Ng et al. 2018).

7.10 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 morality. 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 production (Michniacki et al. 2019).

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 efficacious (Obut et al. 2016).

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) (Thompson et al. 2017; Panoskaltsis-Mortari et al. 2011). 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.

7.11 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 cytopenias (Michniacki et al. 2019), and in an attempt to reduce chronic GVHD incidence by suppressing allogeneic donor B cell immunity (Arai et al. 2012). Given the propensity for EBV to target B lymphocytes, rituximab is also used to treat post-transplant EBV viremia/reactivation (Poppiti et al. 2016). 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 described (Henrickson et al. 2016). Fever and infusion-related hypersensitivity

may occur but can be prevented with pre-infusion acetaminophen, diphenhydramine, and/or corticosteroid administration.

7.12 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 cells (Michniacki et al. 2019). 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.

7.13 Eculizumab

Inactivation of the terminal complement component CD5 by eculizumab can lead to a drastic improvement in patients suffering from post-transplant TMA (Obut et al. 2016). 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 eculizumab (Henrickson et al. 2016).

8 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.

Acknowledgements D.P. is currently supported by a St. Baldrick's Foundation Hope from Harper Fellowship and a Hyundai Hope on Wheels Young Investigator and S.W.C. is currently supported by NHLBI grant R01HL146354, NCI grant R01CA249211, and NHLBI grant K24HL156896.

References

Acevedo A et al (1991) Identification of natural killer (NK) cells in lesions of human cutaneous graft-versus-host disease: expression of a novel NK-associated surface antigen (Kp43) in mononuclear infiltrates. J Invest Dermatol 97:659–666

Andrlová H, van den Brink MRM, Markey KA (2020) An unconventional view of T cell reconstitution after allogeneic hematopoietic cell transplantation. Front Oncol 10:608923

Antin JH, Ferrara JL (1992) Cytokine dysregulation and acute graft-versus-host disease. Blood 80:2964–2968

Arai S et al (2012) Prophylactic rituximab after allogeneic transplantation decreases B-cell alloimmunity with low chronic GVHD incidence. Blood 119:6145–6154

Arai Y, Jo T, Matsui H, Kondo T, Takaori-Kondo A (2017) Efficacy of antithymocyte globulin for allogeneic hematopoietic cell transplantation: a systematic review and meta-analysis. Leuk Lymphoma 58:1840–1848

Ballen KK, Gluckman E, Broxmeyer HE (2013) Umbilical cord blood transplantation: the first 25 years and beyond. Blood 122:491–498

Ben Youssef G et al (2018) Ontogeny of human mucosal-associated invariant T cells and related T cell subsets. J Exp Med 215:459–479

Bhattacharyya A et al (2018) Graft-derived reconstitution of mucosal-associated invariant T cells after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 24:242–251

Blazar BR et al (1996) Lethal murine graft-versus-host disease induced by donor gamma/delta expressing T cells with specificity for host nonclassical major histocompatibility complex class Ib antigens. Blood 87:827–837

Bleakley M et al (2015) Outcomes of acute leukemia patients transplanted with naive T cell-depleted stem cell grafts. J Clin Invest 125:2677–2689

Bolaños-Meade J et al (2005) Pentostatin in steroid-refractory acute graft-versus-host disease. J Clin Oncol 23:2661–2668

Bruce DW et al (2017) Type 2 innate lymphoid cells treat and prevent acute gastrointestinal graft-versus-host disease. J Clin Invest 127:1813–1825

Brunstein CG et al (2016) Umbilical cord blood-derived T regulatory cells to prevent GVHD: kinetics, toxicity profile, and clinical effect. Blood 127:1044–1051

Chaidos A et al (2012) Graft invariant natural killer T-cell dose predicts risk of acute graft-versus-host disease in allogeneic hematopoietic stem cell transplantation. Blood 119:5030–5036

Chen BJ et al (2007) Inability of memory T cells to induce graft-versus-host disease is a result of an abortive alloresponse. Blood 109:3115–3123

Chen Y-B et al (2017a) Increased Foxp3+Helios+ regulatory T cells and decreased acute graft-versus-host disease after allogeneic bone marrow transplantation in patients receiving sirolimus and RGI-2001, an activator of invariant natural killer T cells. Biol Blood Marrow Transplant 23:625–634

Chen Y-B et al (2017b) Phase 1 multicenter trial of brentuximab vedotin for steroid-refractory acute graft-versus-host disease. Blood 129:3256–3261

Cheng Q et al (2015) The S1P1 receptor-selective agonist CYM-5442 reduces the severity of acute GVHD by inhibiting macrophage recruitment. Cell Mol Immunol 12:681–691

Cheung TS et al (2020) Mesenchymal stromal cells for graft versus host disease: mechanism-based biomarkers. Front Immunol 11:1338

Chiang K-Y, Abhyankar S, Bridges K, Godder K, Henslee-Downey JP (2002) Recombinant human tumor necrosis factor receptor fusion protein as complementary treatment for chronic graft-versus-host disease. Transplantation 73:665–667

Chinen J, Shearer WT (2010) Secondary immunodeficiencies, including HIV infection. J Allergy Clin Immunol 125:S195–S203
Choi S, Reddy P (2011) HDAC inhibition and graft versus host disease. Mol Med Camb Mass 17:404–416
Choi SW, Reddy P (2014) Current and emerging strategies for the prevention of graft versus host disease. Nat Rev Clin Oncol 11:536–547
Choi SW, Levine JE, Ferrara JLM (2010) Pathogenesis and management of graft versus host disease. Immunol Allergy Clin N Am 30:75–101
Choi I et al (2014a) Donor-derived natural killer cells infused after human leukocyte antigen-haploidentical hematopoietic cell transplantation: a dose-escalation study. Biol Blood Marrow Transplant 20:696–704
Choi SW et al (2014b) Vorinostat plus tacrolimus and mycophenolate to prevent graft-versus-host disease after related-donor reduced-intensity conditioning allogeneic haemopoietic stem-cell transplantation: a phase 1/2 trial. Lancet Oncol 15:87–95
Christopeit M et al (2009) Rituximab reduces the incidence of acute graft-versus-host disease. Blood 113:3130–3131
Chung J et al (2017) Fibroblastic niches prime T cell alloimmunity through delta-like notch ligands. J Clin Invest 127:1574–1588
Cooley S et al (2005) KIR reconstitution is altered by T cells in the graft and correlates with clinical outcomes after unrelated donor transplantation. Blood 106:4370–4376
Cuny GD, Suebsuwong C, Ray SS (2017) Inosine-5′-monophosphate dehydrogenase (IMPDH) inhibitors: a patent and scientific literature review (2002-2016). Expert Opin Ther Pat 27:677–690
de Witte MA et al (2021) αβ T-cell graft depletion for allogeneic HSCT in adults with hematological malignancies. Blood Adv 5:240–249
Dehn J et al (2019) Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. Blood 134:924–934
Di Ianni M et al (2011) Tregs prevent GVHD and promote immune reconstitution in HLA-haploidentical transplantation. Blood 117:3921–3928
Divito SJ et al (2020) Peripheral host T cells survive hematopoietic stem cell transplantation and promote graft-versus-host disease. J Clin Invest 130:4624–4636
Drobyski WR et al (2011) Tocilizumab for the treatment of steroid refractory graft-versus-host disease. Biol Blood Marrow Transplant 17:1862–1868
Du W, Cao X (2018) Cytotoxic pathways in allogeneic hematopoietic cell transplantation. Front Immunol 9:2979
Eapen M et al (2011) Effect of donor-recipient HLA matching at HLA A, B, C, and DRB1 on outcomes after umbilical-cord blood transplantation for leukaemia and myelodysplastic syndrome: a retrospective analysis. Lancet Oncol 12:1214–1221
Eapen M et al (2017) Allele-level HLA matching for umbilical cord blood transplantation for non-malignant diseases in children: a retrospective analysis. Lancet Haematol. 4:e325–e333
Elias S, Rudensky AY (2019) Therapeutic use of regulatory T cells for graft-versus-host disease. Br J Haematol 187:25–38
Fan Q et al (2017) Superior GVHD-free, relapse-free survival for G-BM to G-PBSC grafts is associated with higher MDSCs content in allografting for patients with acute leukemia. J Hematol Oncol 10:135
Farag SS et al (2021) Dipeptidyl peptidase 4 inhibition for prophylaxis of acute graft-versus-host disease. N Engl J Med 384:11–19
Ferrara JLM, Levine JE, Reddy P, Holler E (2009) Graft-versus-host disease. Lancet Lond Engl 373:1550–1561
Fløisand Y et al (2019) Safety and effectiveness of vedolizumab in patients with steroid-refractory gastrointestinal acute graft-versus-host disease: a retrospective record review. Biol Blood Marrow Transplant 25:720–727

Flowers MED et al (2011) Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood 117:3214–3219
Fu J, Heinrichs J, Yu X-Z (2014) Helper T-cell differentiation in graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Arch Immunol Ther Exp 62:277–301
Fu J et al (2015) T-bet is critical for the development of acute graft-versus-host disease through controlling T-cell differentiation and function. J Immunol 194:388–397
Furlan SN et al (2020) IL-2 enhances ex vivo–expanded regulatory T-cell persistence after adoptive transfer. Blood Adv 4:1594–1605
Gatza E, Reddy P, Choi SW (2020) Prevention and treatment of acute graft-versus-host disease in children, adolescents, and young adults. Biol Blood Marrow Transplant 26:e101–e112
Gaud G, Lesourne R, Love PE (2018) Regulatory mechanisms in T cell receptor signalling. Nat Rev Immunol 18:485–497
Gergoudis SC et al (2020) Biomarker-guided preemption of steroid-refractory graft-versus-host disease with α-1-antitrypsin. Blood Adv 4:6098–6105
Ghansah T et al (2004) Expansion of myeloid suppressor cells in SHIP-deficient mice represses allogeneic T cell responses. J Immunol 173:7324–7330
Glucksberg H et al (1974) Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 18:295–304
Gooptu M, Koreth J (2020) Translational and clinical advances in acute graft-versus-host disease. Haematologica 105:2550–2560
Grube M et al (2016) Risk factors and outcome of chronic graft-versus-host disease after allogeneic stem cell transplantation-results from a single-center observational study. Biol Blood Marrow Transplant 22:1781–1791
Guillén FJ et al (1986) Acute cutaneous graft-versus-host disease to minor histocompatibility antigens in a murine model. Evidence that large granular lymphocytes are effector cells in the immune response. Lab Investig J Tech Methods Pathol 55:35–42
Hahn T et al (2008) Risk factors for acute graft-versus-host disease after human leukocyte antigen-identical sibling transplants for adults with leukemia. J Clin Oncol 26:5728–5734
Haimes H et al (2019) Impact of skin biopsy on the management of acute graft-versus-host disease in a pediatric population. Pediatr Dermatol 36:455–459
Hanash AM et al (2012) Interleukin-22 protects intestinal stem cells from immune-mediated tissue damage and regulates sensitivity to graft versus host disease. Immunity 37:339–350
Hartwell MJ et al (2017) An early-biomarker algorithm predicts lethal graft-versus-host disease and survival. JCI Insight 2:e89798
Hashimoto D et al (2011) Pretransplant CSF-1 therapy expands recipient macrophages and ameliorates GVHD after allogeneic hematopoietic cell transplantation. J Exp Med 208:1069–1082
Hayase E et al (2017) R-Spondin1 expands Paneth cells and prevents dysbiosis induced by graft-versus-host disease. J Exp Med 214:3507–3518
Heidt S et al (2010) Calcineurin inhibitors affect B cell antibody responses indirectly by interfering with T cell help. Clin Exp Immunol 159:199–207
Henrickson SE, Ruffner MA, Kwan M (2016) Unintended immunological consequences of biologic therapy. Curr Allergy Asthma Rep 16:46
Highfill SL et al (2010) Bone marrow myeloid-derived suppressor cells (MDSCs) inhibit graft-versus-host disease (GVHD) via an arginase-1-dependent mechanism that is up-regulated by interleukin-13. Blood 116:5738–5747
Hill GR, Koyama M (2020) Cytokines and costimulation in acute graft-versus-host disease. Blood 136:418–428
Hill GR, Betts BC, Tkachev V, Kean LS, Blazar BR (2021) Current concepts and advances in graft-versus-host disease immunology. Annu Rev Immunol 39:19–49
Holler E et al (1990) Increased serum levels of tumor necrosis factor alpha precede major complications of bone marrow transplantation. Blood 75:1011–1016

Hołowiecki J (2008) Indications for hematopoietic stem cell transplantation. Pol Arch Med Wewn 118:658–663
Holtan SG, Weisdorf DJ (2017) Vorinostat is victorious in GVHD prevention. Blood 130:1690–1691
Holtan SG et al (2019) Stress responses, M2 macrophages, and a distinct microbial signature in fatal intestinal acute graft-versus-host disease. JCI Insight 5:e129762
Hong Y-Q, Wan B, Li X-F (2020) Macrophage regulation of graft-vs-host disease. World J Clin Cases 8:1793–1805
Hu Y et al (2017) Regulatory B cells promote graft-versus-host disease prevention and maintain graft-versus-leukemia activity following allogeneic bone marrow transplantation. Onco Targets Ther 6:e1284721
Huse M (2009) The T-cell-receptor signaling network. J Cell Sci 122:1269–1273
Iori AP et al (2008) B-cell concentration in the apheretic product predicts acute graft-versus-host disease and treatment-related mortality of allogeneic peripheral blood stem cell transplantation. Transplantation 85:386–390
Jagasia M et al (2012) Risk factors for acute GVHD and survival after hematopoietic cell transplantation. Blood 119:296–307
Jagasia MH et al (2015) National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. the 2014 diagnosis and staging working group report. Biol Blood Marrow Transplant 21:389–401.e1
Jaiswal SR et al (2017) CD56-enriched donor cell infusion after post-transplantation cyclophosphamide for haploidentical transplantation of advanced myeloid malignancies is associated with prompt reconstitution of mature natural killer cells and regulatory T cells with reduced incidence of acute graft versus host disease: a pilot study. Cytotherapy 19:531–542
Jankovic D et al (2013) The Nlrp3 inflammasome regulates acute graft-versus-host disease. J Exp Med 210:1899–1910
Kamble R, Oholendt M, Carrum G (2006) Rituximab responsive refractory acute graft-versus-host disease. Biol Blood Marrow Transplant 12:1201–1202
Kanakry CG et al (2013) Aldehyde dehydrogenase expression drives human regulatory T cell resistance to posttransplantation cyclophosphamide. Sci Transl Med 5:211ra157
Kawaguchi K et al (2018) Influence of post-transplant mucosal-associated invariant T cell recovery on the development of acute graft-versus-host disease in allogeneic bone marrow transplantation. Int J Hematol 108:66–75
Kebriaei P et al (2020) A phase 3 randomized study of remestemcel-L versus placebo added to second-line therapy in patients with steroid-refractory acute graft-versus-host disease. Biol Blood Marrow Transplant 26:835–844
Kennedy GA et al (2014) Addition of interleukin-6 inhibition with tocilizumab to standard graft-versus-host disease prophylaxis after allogeneic stem-cell transplantation: a phase 1/2 trial. Lancet Oncol 15:1451–1459
Kennedy GA et al (2021) A phase 3 double-blind study of the addition of tocilizumab vs placebo to cyclosporin/methotrexate GVHD prophylaxis. Blood 137:1970–1979
Khandelwal P et al (2021) Graft-versus-host disease prophylaxis with abatacept reduces severe acute graft-versus-host disease in allogeneic hematopoietic stem cell transplant for beta-thalassemia major with busulfan, fludarabine, and thiotepa. Transplantation 105:891–896
Khouri IF et al (2008) Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. Blood 111:5530–5536
Koehn BH et al (2015) GVHD-associated, inflammasome-mediated loss of function in adoptively transferred myeloid-derived suppressor cells. Blood 126:1621–1628
Koehn BH et al (2019) Danger-associated extracellular ATP counters MDSC therapeutic efficacy in acute GVHD. Blood 134:1670–1682
Koreth J et al (2011) Interleukin-2 and regulatory T cells in graft-versus-host disease. N Engl J Med 365:2055–2066

Koyama M et al (2011) Recipient nonhematopoietic antigen-presenting cells are sufficient to induce lethal acute graft-versus-host disease. Nat Med 18:135–142
Koyama M et al (2015) Donor colonic CD103+ dendritic cells determine the severity of acute graft-versus-host disease. J Exp Med 212:1303–1321
Koyama M et al (2019) MHC class II antigen presentation by the intestinal epithelium initiates graft-versus-host disease and is influenced by the microbiota. Immunity 51:885–898.e7
Kurtzberg J et al (2020) A phase 3, single-arm, prospective study of remestemcel-L, ex vivo culture-expanded adult human mesenchymal stromal cells for the treatment of pediatric patients who failed to respond to steroid treatment for acute graft-versus-host disease. Biol Blood Marrow Transplant 26:845–854
Lee SJ et al (2015) Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 response criteria working group report. Biol Blood Marrow Transplant 21:984–999
Levine JE et al (2008) Etanercept plus methylprednisolone as initial therapy for acute graft-versus-host disease. Blood 111:2470–2475
Levine JE et al (2015) A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study. Lancet Haematol 2:e21–e29
Li A, Abraham C, Wang Y, Zhang Y (2020) New insights into the basic biology of acute graft-versus-host-disease. Haematologica 105:2540–2549
Locatelli F et al (2017) Outcome of children with acute leukemia given HLA-haploidentical HSCT after αβ T-cell and B-cell depletion. Blood 130:677–685
Loiseau P et al (2007) HLA association with hematopoietic stem cell transplantation outcome: the number of mismatches at HLA-A, -B, -C, -DRB1, or -DQB1 is strongly associated with overall survival. Biol Blood Marrow Transplant 13:965–974
MacMillan ML et al (2020) Validation of Minnesota acute graft-versus-host disease risk score. Haematologica 105:519–524
Maeda Y et al (2005) Critical role of host gammadelta T cells in experimental acute graft-versus-host disease. Blood 106:749–755
Magenau JM et al (2018) α1-Antitrypsin infusion for treatment of steroid-resistant acute graft-versus-host disease. Blood 131:1372–1379
Major-Monfried H et al (2018) MAGIC biomarkers predict long-term outcomes for steroid-resistant acute GVHD. Blood 131:2846–2855
Mancusi A, Piccinelli S, Velardi A, Pierini A (2019) CD4+FOXP3+ regulatory T cell therapies in HLA haploidentical hematopoietic transplantation. Front Immunol 10:2901
Marcondes AM et al (2014) α-1-antitrypsin (AAT)-modified donor cells suppress GVHD but enhance the GVL effect: a role for mitochondrial bioenergetics. Blood 124:2881–2891
Martelli MF et al (2014) HLA-haploidentical transplantation with regulatory and conventional T-cell adoptive immunotherapy prevents acute leukemia relapse. Blood 124:638–644
Martin PJ (2021) Sitagliptin to prevent acute graft-versus-host disease. N Engl J Med 384:70–71
Maschmeyer G et al (2019) Infections associated with immunotherapeutic and molecular targeted agents in hematology and oncology. A position paper by the European conference on infections in leukemia (ECIL). Leukemia 33:844–862
Mathewson ND et al (2016) Gut microbiome-derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease. Nat Immunol 17:505–513
Matsuoka K et al (2013) Low-dose interleukin-2 therapy restores regulatory T cell homeostasis in patients with chronic graft-versus-host disease. Sci Transl Med 5:179ra43
McCurdy SR, Luznik L (2019) How we perform haploidentical stem cell transplantation with posttransplant cyclophosphamide. Hematol Am Soc Hematol Educ Program 2019:513–521
Meyer EH et al (2019) Transplantation of donor grafts with defined ratio of conventional and regulatory T cells in HLA-matched recipients. JCI Insight 4:e127244

Michniacki TF, Ebens CL, Choi SW (2019) Immune-mediated cytopenias after hematopoietic cell transplantation: pathophysiology, clinical manifestations, diagnosis, and treatment strategies. Curr Oncol Rep 21:87

Michonneau D et al (2009) Influence of bone marrow graft B lymphocyte subsets on outcome after HLA-identical sibling transplants. Br J Haematol 145:107–114

Moy RH et al (2017) Clinical and immunologic impact of CCR5 blockade in graft-versus-host disease prophylaxis. Blood 129:906–916

Munneke JM et al (2014) Activated innate lymphoid cells are associated with a reduced susceptibility to graft-versus-host disease. Blood 124:812–821

Murphy WJ, Bennett M, Kumar V, Longo DL (1992) Donor-type activated natural killer cells promote marrow engraftment and B cell development during allogeneic bone marrow transplantation. J Immunol 148:2953–2960

Nakasone H et al (2015) Impact of conditioning intensity and TBI on acute GVHD after hematopoietic cell transplantation. Bone Marrow Transplant 50:559–565

Nash RA et al (1996) FK506 in combination with methotrexate for the prevention of graft-versus-host disease after marrow transplantation from matched unrelated donors. Blood 88:3634–3641

Ng SC et al (2018) Low frequency of opportunistic infections in patients receiving vedolizumab in clinical trials and post-marketing setting. Inflamm Bowel Dis 24:2431–2441

Nguyen VH et al (2007) In vivo dynamics of regulatory T-cell trafficking and survival predict effective strategies to control graft-versus-host disease following allogeneic transplantation. Blood 109:2649–2656

Ngwube A et al (2020) Abatacept is effective as GVHD prophylaxis in unrelated donor stem cell transplantation for children with severe sickle cell disease. Blood Adv 4:3894–3899

Nieves EC et al (2017) STAT3 expression in host myeloid cells controls GVHD severity. Biol Blood Marrow Transplant 23:1622–1630

Nishiwaki S et al (2014) Dexamethasone palmitate ameliorates macrophages-rich graft-versus-host disease by inhibiting macrophage functions. PLoS One 9:e96252

Obut F, Kasinath V, Abdi R (2016) Post-bone marrow transplant thrombotic microangiopathy. Bone Marrow Transplant 51:891–897

Olson JA et al (2010) NK cells mediate reduction of GVHD by inhibiting activated, alloreactive T cells while retaining GVT effects. Blood 115:4293–4301

Panoskaltsis-Mortari A et al (2011) An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. Am J Respir Crit Care Med 183:1262–1279

Passweg JR et al (2004) Purified donor NK-lymphocyte infusion to consolidate engraftment after haploidentical stem cell transplantation. Leukemia 18:1835–1838

Poppiti K, Lin A, Adel NG, Hilden P, Castro-Malaspina H (2016) Outcomes of rituximab for EBV viremia/post-transplant lymphoproliferative disease in CD34+ selected allogeneic hematopoietic stem cell transplantation. Blood 128:4623–4623

Przepiorka D et al (1995) 1994 consensus conference on acute GVHD grading. Bone Marrow Transplant 15:825–828

Pulsipher MA et al (2014) The addition of sirolimus to tacrolimus/methotrexate GVHD prophylaxis in children with ALL: a phase 3 children's oncology group/pediatric blood and marrow transplant consortium trial. Blood 123:2017–2025

Rafei H, Jenq RR (2020) Microbiome-intestine cross talk during acute graft-versus-host disease. Blood 136:401–409

Ratanatharathorn V et al (2009) Prior rituximab correlates with less acute graft-versus-host disease and better survival in B-cell lymphoma patients who received allogeneic peripheral blood stem cell transplantation (PBSCT). Br J Haematol 145:816–824

Reddy P (2012) GVHD prevention: an ounce is better than a pound. Biol Blood Marrow Transplant 18:S17–S26

Rodriguez-Otero P et al (2012) Fecal calprotectin and alpha-1 antitrypsin predict severity and response to corticosteroids in gastrointestinal graft-versus-host disease. Blood 119:5909–5917

Ross SH, Cantrell DA (2018) Signaling and function of interleukin-2 in T lymphocytes. Annu Rev Immunol 36:411–433
Roy J, Platt JL, Weisdorf DJ (1993) The immunopathology of upper gastrointestinal acute graft-versus-host disease. Lymphoid cells and endothelial adhesion molecules. Transplantation 55:572–578
Ruggeri L et al (2002) Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science 295:2097–2100
Ruutu T et al (2014) Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. Bone Marrow Transplant 49:168–173
Saidu NEB et al (2020) New approaches for the treatment of chronic graft-versus-host disease: current status and future directions. Front Immunol 11:578314
Salomon BL et al (2018) Tumor necrosis factor α and regulatory T cells in oncoimmunology. Front Immunol 9:444
Sato K, Yamashita N, Yamashita N, Baba M, Matsuyama T (2003) Regulatory dendritic cells protect mice from murine acute graft-versus-host disease and leukemia relapse. Immunity 18:367–379
Schneidawind D et al (2014) CD4+ invariant natural killer T cells protect from murine GVHD lethality through expansion of donor CD4+CD25+FoxP3+ regulatory T cells. Blood 124:3320–3328
Schneidawind D et al (2015) Third-party CD4+ invariant natural killer T cells protect from murine GVHD lethality. Blood 125:3491–3500
Schnitzler M, Hasskarl J, Egger M, Bertz H, Finke J (2009) Successful treatment of severe acute intestinal graft-versus-host resistant to systemic and topical steroids with alemtuzumab. Biol Blood Marrow Transplant 15:910–918
Schultz KR, Paquet J, Bader S, HayGlass KT (1995) Requirement for B cells in T cell priming to minor histocompatibility antigens and development of graft-versus-host disease. Bone Marrow Transplant 16:289–295
Schwab L et al (2014) Neutrophil granulocytes recruited upon translocation of intestinal bacteria enhance graft-versus-host disease via tissue damage. Nat Med 20:648–654
Shah NN et al (2015) Acute GVHD in patients receiving IL-15/4-1BBL activated NK cells following T-cell-depleted stem cell transplantation. Blood 125:784–792
Shao L et al (2019) An essential role of innate lymphoid cells in the pathophysiology of graft-vs.-host disease. Front Immunol 10:1233
Shimabukuro-Vornhagen A, Hallek MJ, Storb RF, von Bergwelt-Baildon MS (2009) The role of B cells in the pathogenesis of graft-versus-host disease. Blood 114:4919–4927
Shimoni A et al (2003) Rituximab reduces relapse risk after allogeneic and autologous stem cell transplantation in patients with high-risk aggressive non-Hodgkin's lymphoma. Br J Haematol 122:457–464
Shlomchik WD (2007) Graft-versus-host disease. Nat Rev Immunol 7:340–352
Si S, Teachey DT (2020) Spotlight on tocilizumab in the treatment of CAR-T-cell-induced cytokine release syndrome: clinical evidence to date. Ther Clin Risk Manag 16:705–714
Simonetta F, Alvarez M, Negrin RS (2017) Natural killer cells in graft-versus-host-disease after allogeneic hematopoietic cell transplantation. Front Immunol 8:465
Stein-Thoeringer CK et al (2019) Lactose drives Enterococcus expansion to promote graft-versus-host disease. Science 366:1143–1149
Strobl J et al (2020) Long-term skin-resident memory T cells proliferate in situ and are involved in human graft-versus-host disease. Sci Transl Med 12:eabb7028
Summers C, Sheth VS, Bleakley M (2020) Minor histocompatibility antigen-specific T cells. Front Pediatr 8:284
Swimm A et al (2018) Indoles derived from intestinal microbiota act via type I interferon signaling to limit graft-versus-host disease. Blood 132:2506–2519
Takashima S et al (2011) The Wnt agonist R-spondin1 regulates systemic graft-versus-host disease by protecting intestinal stem cells. J Exp Med 208:285–294

Takashima S et al (2019) T cell-derived interferon-γ programs stem cell death in immune-mediated intestinal damage. Sci Immunol 4:eaay8556
Tawara I et al (2012) Alpha-1-antitrypsin monotherapy reduces graft-versus-host disease after experimental allogeneic bone marrow transplantation. Proc Natl Acad Sci U S A 109:564–569
Taylor PA, Lees CJ, Blazar BR (2002) The infusion of ex vivo activated and expanded CD4(+) CD25(+) immune regulatory cells inhibits graft-versus-host disease lethality. Blood 99:3493–3499
Thompson J et al (2017) Etanercept and corticosteroid therapy for the treatment of late-onset idiopathic pneumonia syndrome. Biol Blood Marrow Transplant 23:1955–1960
Toubai T et al (2012) Induction of acute GVHD by sex-mismatched H-Y antigens in the absence of functional radiosensitive host hematopoietic–derived antigen-presenting cells. Blood 119:3844–3853
Trzonkowski P et al (2009) First-in-man clinical results of the treatment of patients with graft versus host disease with human ex vivo expanded CD4+CD25+CD127- T regulatory cells. Clin Immunol 133:22–26
Varelias A et al (2018) Recipient mucosal-associated invariant T cells control GVHD within the colon. J Clin Invest 128:1919–1936
Vendramin A et al (2014) Graft monocytic myeloid-derived suppressor cell content predicts the risk of acute graft-versus-host disease after allogeneic transplantation of granulocyte colony-stimulating factor-mobilized peripheral blood stem cells. Biol Blood Marrow Transplant 20:2049–2055
Voermans C, Hazenberg MD (2020) Cellular therapies for graft-versus-host disease: a tale of tissue repair and tolerance. Blood 136:410–417
Wachsmuth LP et al (2019) Post-transplantation cyclophosphamide prevents graft-versus-host disease by inducing alloreactive T cell dysfunction and suppression. J Clin Invest 129:2357–2373
Wang K et al (2019) Early myeloid-derived suppressor cells (HLA-DR-/lowCD33+CD16-) expanded by granulocyte colony-stimulating factor prevent acute graft-versus-host disease (GVHD) in humanized mouse and might contribute to lower GVHD in patients post allo-HSCT. J Hematol Oncol 12:31
Weber M et al (2014) Donor and host B cell-derived IL-10 contributes to suppression of graft-versus-host disease. Eur J Immunol 44:1857–1865
Welniak LA, Blazar BR, Anver MR, Wiltrout RH, Murphy WJ (2000) Opposing roles of interferon-gamma on CD4+ T cell-mediated graft-versus-host disease: effects of conditioning. Biol Blood Marrow Transplant 6:604–612
Wen Q et al (2019) G-CSF-induced macrophage polarization and mobilization may prevent acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 54:1419–1433
Whitehouse G et al (2017) IL-2 therapy restores regulatory T-cell dysfunction induced by calcineurin inhibitors. Proc Natl Acad Sci 114:7083–7088
Wilhelm K et al (2010) Graft-versus-host disease is enhanced by extracellular ATP activating P2X7R. Nat Med 16:1434–1438
Xun C, Brown SA, Jennings CD, Henslee-Downey PJ, Thompson JS (1993) Acute graft-versus-host-like disease induced by transplantation of human activated natural killer cells into SCID mice. Transplantation 56:409–417
Xun CQ, Thompson JS, Jennings CD, Brown SA (1995) The effect of human IL-2-activated natural killer and T cells on graft-versus-host disease and graft-versus-leukemia in SCID mice bearing human leukemic cells. Transplantation 60:821–827
Yi T et al (2009) Reciprocal differentiation and tissue-specific pathogenesis of Th1, Th2, and Th17 cells in graft-versus-host disease. Blood 114:3101–3112
Youssef J, Novosad S, Winthrop K (2016) Infection risk and safety of corticosteroid use. Rheum Dis Clin N Am 42:157–176

Yu H, Tian Y, Wang Y, Mineishi S, Zhang Y (2019) Dendritic cell regulation of graft-vs.-host disease: immunostimulation and tolerance. Front Immunol 10:93

Zeiser R, Blazar BR (2017a) Acute graft-versus-host disease - biologic process, prevention, and therapy. N Engl J Med 377:2167–2179

Zeiser R, Blazar BR (2017b) Pathophysiology of chronic graft-versus-host disease and therapeutic targets. N Engl J Med 377:2565–2579

Zeiser R et al (2006) Inhibition of CD4+CD25+ regulatory T-cell function by calcineurin-dependent interleukin-2 production. Blood 108:390–399

Zeiser R et al (2020) Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. N Engl J Med 382:1800–1810

Zhang J et al (2019) The mechanistic study behind suppression of GVHD while retaining GVL activities by myeloid-derived suppressor cells. Leukemia 33:2078–2089

Zhao D et al (2018) Survival signal REG3α prevents crypt apoptosis to control acute gastrointestinal graft-versus-host disease. J Clin Invest 128:4970–4979

Zhou Y, Barnett MJ, Rivers JK (2000) Clinical significance of skin biopsies in the diagnosis and management of graft-vs-host disease in early postallogeneic bone marrow transplantation. Arch Dermatol 136:717–721