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The delicate balance of graft versus leukemia and graft versus host disease after allogeneic hematopoietic stem cell transplantation

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Abstract

Introduction: The curative basis of allogeneic hematopoietic stem cell transplantation (HSCT) relies in part upon the graft versus leukemia (GvL) effect, whereby donor immune cells recognize and eliminate recipient malignant cells. However, alloreactivity of donor cells against recipient tissues may also be deleterious. Chronic graft versus host disease (cGvHD) is an immunologic phenomenon wherein alloreactive donor T cells aberrantly react against host tissues, leading to damaging inflammatory symptoms.

Areas Covered: Here, we discuss biological insights into GvL and cGvHD and strategies to balance the prevention of GvHD with maintenance of GvL in modern HSCT.

Expert Opinion/Commentary: Relapse remains the leading cause of mortality after HSCT with rates as high as 40% for some diseases. GvHD is a major cause of morbidity after HSCT, occurring in up to half of patients and responsible for 15–20% of deaths after HSCT. Intriguingly, the development of chronic GvHD may be linked to lower relapse rates after HSCT, suggesting that GvL and GvHD may be complementary sides of the immunologic foundation of HSCT. The ability to fine tune the balance of GvL and GvHD will lead to improvements in survival, relapse rates, and quality of life for patients undergoing HSCT.

Keywords

Chronic graft versus host disease; relapse; GvHD; GvL; HSCT

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Declaration of interest

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1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has the potential to induce long-term remission in patients with hematologic malignancies mediated in part through graft versus leukemia (GvL) activity of donor immune cells against recipient malignant cells [1.] Relapse remains the most substantial challenge in HSCT and the major cause of mortality in patients, occurring in up to 40% of cases [2]. The GvL effect can be leveraged to re-introduce remission in some patients through strategies such as immunosuppression taper or donor lymphocyte infusion (DLI); however, success rates of these strategies are highly variable. For example, DLI results in ~ 80% response rate for chronic myelogenous leukemia (CML) whereas patients with acute myeloid leukemia (AML) only respond in ~ 20% of the cases [3]. While such donor alloreactivity is beneficial in maintaining remission, excessive alloreactivity of donor lymphocytes can also mediate Graft versus Host Disease (GvHD), leading to autoimmune-like inflammation. GvHD is a major cause of morbidity and mortality after HSCT, and its chronic form (cGvHD) has been particularly difficult to manage, owing to few effective available therapies. In recent years, several new therapies have become available for better prevention and treatment of cGvHD. Curiously, these treatments appear to act through different biological pathways, underscoring both the complex nature of the disease and the limitations of our understanding of its cellular and molecular underpinnings. Similarly, the true physiology of GvL remains elusive despite long standing clinical demonstration of this phenomenon through the ability of donor lymphocyte infusions (DLI) alone to restore remission in patients who have relapsed after HSCT. Indeed, it remains unclear whether GvL targets specific leukemia antigens in particular or whether this is due to targeting recipient hematopoietic elements in general.

The balance between GvHD and GvL is crucial in determining the clinical outcome of HSCT. The presence of GvL is associated with a reduced risk of relapse and improved survival, while severe GvHD can cause significant morbidity and mortality [4,5]. However, GvHD and GvL are closely linked and may be at least in part driven by similar immune cell populations and mechanisms [6-8]. Moreover, immunosuppressive drugs used to prevent GvHD may also impair GvL, increasing the risk of relapse [9-11]. Conversely, strategies to enhance GvL may increase the risk of GvHD [12,13]. For instance, immune suppression taper for relapse after HSCT was sufficient to re-instate remission in one-third of patients, and 97% of those who responded had development or progression of acute or chronic GvHD [14]. Similarly, a retrospective analysis of prognostic factors for favorable response after post-HSCT disease relapse demonstrated that induction of GvHD after relapse was associated with improved overall survival, and that this was independent of whether GvHD was induced in the presence or absence of adoptive cellular immunotherapy [15].

Multiple studies have demonstrated a relationship between the presence of GvHD and lower relapse rates [16-19]. One retrospective study demonstrated a link between the development of grade 1–2 acute aGvHD and improved overall survival for adult T cell leukemia [20]. A similar trend was found for patients with CMML undergoing HSCT, with an association between aGvHD and improved overall survival identified by univariate analysis and a stronger association with cGvHD and better overall survival in both univariate and multivariable analysis [21]. The link between GvHD and reduced relapse risk appears to be

stronger for cGvHD compared to aGvHD, with several studies identifying a beneficial effect of the development of cGvHD on protection from later relapse, particularly for patients receiving reduced intensity conditioning regimens [22-24]. The mechanism underlying the association between cGvHD and reduced relapse risk is not clear. One hypothesis is that immune dysregulation caused by cGvHD may lead to the activation and expansion of immune effector cells, which may eliminate residual malignant cells [25,26]. Additionally, cGvHD may stimulate the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), promoting direct anti-tumor effects. Preclinical studies have also provided evidence for the GvL effect. In a mouse model of AML, allogeneic HSCT was found to be more effective than syngeneic HSCT in eradicating the leukemia cells. The effect was again found to be dependent on the donor T cells, indicating a role for GvL [27], a finding further underscored by studies in humans [16].

Several factors can affect the balance between GvHD and GvL, including the type and intensity of conditioning regimens used before HSCT, the degree of HLA mismatch between the donor and recipient, and the nature of the malignant disease. Strategies to improve the balance between GvHD and GvL are needed to improve both survival and quality of life outcomes for patients after HSCT.

2. Pathogenesis of cGvhd

The initial trigger for cGvHD is thought to be tissue damage caused by conditioning therapy or infection, which leads to the release of host antigens that activate donor T cells. Donor T cells then migrate to target organs, where they induce inflammation, fibrosis, and tissue damage. In addition to T cells, B cells, natural killer cells, and dendritic cells have all been implicated in the pathogenesis of cGvHD. Chronic GvHD is characterized by the accumulation of extracellular matrix proteins, including collagen, fibronectin, and proteoglycans, leading to tissue fibrosis [28-30]. Studies have shown that TGF-β and other profibrotic cytokines are upregulated in cGvHD, contributing to the development of fibrosis [28, 31-34]. Several mechanisms have been proposed to explain the pathophysiology of cGvHD.

2.1. Conventional T cells

A wide range of T cell phenotypic and functional subsets may contribute to GvHD pathogenesis. For example, antigen stimulated CD8+ T cells from HSCT patients were shown to develop into CD4+/CD8+ double positive cells that were sufficient to mediate GvHD pathogenesis in mouse xenograft models [35]. Histopathological examination of mucocutaneous biopsies from patients with cGvHD have demonstrated infiltration of cytotoxic CD8+ T cells [36] as well as CD4+ cells [37], suggesting a role for direct cytotoxicity. T cells may also mediate cGvHD pathogenesis indirectly through production and secretion of cytokines. Th1 and Th2 cytokines, such as IFN-γ and IL-4, are upregulated in cGvHD (Figure 1). Th1 cells are responsible for cell-mediated immunity, while Th2 cells mediate humoral immunity. Activated T cells produce interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-17 (IL-17), which recruit and activate other immune cells promoting tissue damage. T cells can also directly damage tissues by killing

cells expressing host antigens through cytotoxic mechanisms. CD4 T cells have also been implicated in driving GvHD pathogenesis in mice through regulation of alloreactivity by nuclear factor erythroid-derived 2-like 2 (NRF2), a transcription factor critical for cellular redox [38]. Mice transplanted with CD4+ T cells deficient for NRF2 experienced less GvHD compared to wild-type, while *Nrf2*$^{-/-}$ donor CD8+ T cells maintained cytotoxic capabilities, suggesting intact graft versus leukemia (GvL) activity. *ATG16L1* is a key autophagy gene, a pathway responsible for mediating intracellular degradation, and deficiency of *ATG16L1* is linked to increased intestinal inflammation and development of inflammatory bowel disease [39,40]. Models of HSCT in *ATG16L1* deficient mice displayed enhanced GvHD with increased T cell proliferation due to increased dendritic cell costimulatory molecule production [41]. T cell alloreactivity driving GvHD has also been linked to deficiency of the short-chain fatty acid receptor GPR109A as well as STAT-3 and ERK1/2 phosphorylation, suggesting these as potential targets for mitigating GvHD pathogenesis [42,43].

Noncanonical T cell subsets are being studied for their impact in mediating GvHD. A recent study found that more diverse intestinal microbiome after HSCT was associated with increased numbers of innate-like mucosal-associated invariant T (MAIT) cells and a subpopulation of circulating γδ T cells, which in turn was associated with a decrease in the incidence of intestinal aGvHD [44].

2.2. Regulatory T cells (tregs)

Tregs are a subset of T cells that play a key role in maintaining immune tolerance and preventing autoimmunity. The number and function of Tregs are reduced in the setting of cGvHD, leading to the loss of tolerance and activation of autoreactive T cells (Figure 1). A decrease in the frequency and absolute number of Tregs has been observed in patients with cGvHD compared to those without cGvHD [45]. Lower Treg numbers at 3 months after HSCT were also associated with increased risk of cGvHD. In mouse models of cGvHD, adoptive transfer of Tregs ameliorates cGvHD [46], a finding further supported by small trials in humans [47-49]. Further, administration of low-dose interleukin-2 (IL-2), which selectively expands Tregs, has been shown to prevent and treat cGvHD in preclinical models.

2.3. B cells

Although cGvHD is thought to be driven primarily by alloreactive T cells, there is evidence to support a role for B cells in driving pathogenesis, likely through the production of autoantibodies against host antigens, such as collagen and keratinocyte antigens. These autoantibodies can promote inflammation and tissue damage in various organs, including the skin, liver, and lungs. High levels of the B-cell activating factor (BAFF) have been identified in patients with active cGvHD [50-53]. In addition, antibodies directed toward Y-chromosome antigens have been observed in male HSCT recipients with grafts from female donors, and antibody titer correlates with GvHD disease severity (Figure 1) [54-57]. This observation has prompted clinical use of B cell targeting monoclonal antibodies for GvHD therapy, though the efficacy of these strategies remains a subject of debate.

2.4. Microbiome dysbiosis and the inflammasome

Recent studies have shown that the microbiome plays a critical role in modulating the immune response and maintaining immune homeostasis. Dysbiosis of the gut microbiome has a well-established association with increased risk of acute GvHD (aGvHD) (Figure 1) [58-61]. More recently, microbiome dysbiosis has been implicated in pathogenesis of cGvHD as well. A mouse model of cGvHD demonstrated that microbiota dysbiosis skews intestinal T cell ratios toward decreased T reg abundance, promoting cGvHD [62]. One study in humans found that patients with higher intestinal abundance of *Prevotella* prior to HSCT or higher abundance of *Akkermansia* and *Streptococcus* at Day 100 after HSCT had higher incidence of cGvHD [63]. Conversely, increased prevalence of intestinal Blautia, a genus of Clostridia, was found to be associated with protection from intestinal GvHD [59]. Dysbiosis may skew gut microbiota-derived short chain fatty acids (SCFAs). Lower circulating concentrations of butyrate and propionate, two microbe-derived SCFAs, have been found in patients at post-HSCT day 100 who developed cGvHD [64].

2.5. The inflammasome

Multiple lines of evidence implicate the inflammasome in GvHD pathogenesis, primarily acute [65]. The inflammasome is a protein complex belonging to the innate immune system that primarily functions to sense and respond to infectious microbial components leading to the production of inflammatory cytokine Interleukin-1b (IL-1b) (Figure 1) [66,67]. Intestinal commensal bacteria and damage-associated molecular patterns (DAMPs) have been shown to initiate NLRP3 inflammasome activation and IL-1b production after conditioning therapy, while blockade of IL-1b signaling mitigates acute GvHD pathogenesis [68,69]. Myeloid derived suppressor cells (MDSCs) with anti-inflammatory properties have been shown to lose suppressive function (and ability to abrogate GvHD) after exposure to inflammasome-activating mediators [70]. More recently, ambient oxygen levels in the intestine have been shown to lead to dysbiosis, promoting intestinal damage mediated by alloreactive T cells in a mechanism dependent upon intestinal HIF-1a and the microbiome [70,71]. In humans, specific single nucleotide polymorphism genotypes of the NLRP3 inflammasome have been linked to greater proclivity for developing acute or chronic GvHD [72]. These preclinical experimental models raise new areas of investigation for translation into clinical therapeutic strategies for GvHD diagnosis and treatment.

3. Strategies for prevention of cGvhd

After decades of research attempting to optimize GvHD prophylaxis regimens, very few strategies have been successful in reducing rates of acute or chronic GvHD. For aGvHD, a recent randomized phase II trial of addition of abatacept to the standard combination of calcineurin inhibitor (CNI) and methotrexate (MTX) demonstrated marked abrogation of grade III-IV aGvHD for recipients of fully HLA-matched HSCT compared to CNI/MTX plus placebo [73]. This promising result recently led to FDA approval of abatacept for aGvHD prophylaxis. Only two strategies have proven to be successful in reducing cGvHD: *in vivo* or *ex vivo* T cell depletion and, more recently, post-transplant cyclophosphamide (PTCy).

3.1. T-cell depletion

T cell depletion (TCD) is a strategy used to prevent cGvHD by removing or suppressing T cells that play a crucial role in the development of GvHD. This approach can be achieved through several *in vivo* serologic methods, such as alemtuzumab or anti-thymocyte/anti-T lymphocyte globulin (ATG/ATLG), often derived from rabbit or horse sera. Alemtuzumab is a monoclonal antibody against CD52, which is present on mature lymphocytes, and has been implemented as an *in vivo* method of T cell depletion. Trials using alemtuzumab as part of the GvHD prophylaxis regimen during HSCT have demonstrated reduced acute and chronic GvHD, acceptable immune reconstitution, and overall similar survival and relapse rates to conventional GvHD prophylaxis regimens [74-76]. Several randomized trials have evaluated ATG/ATLG in combination with standard GvHD prophylaxis (CNI/MTX) versus CNI/MTX alone (or plus placebo) in both the matched related and matched unrelated donor settings and have demonstrated significant reductions in chronic GvHD without negatively impacting relapse rates, although in one of these studies overall survival was lower in the ATLG arm [77-83]. Importantly, lower doses of ATG/ATLG appear to be sufficient for protection from cGvHD, and some studies have found that patients receiving higher doses, while protected from cGvHD, have higher incidence of infections and may have impaired GvL activity [84-86].

Another approach to T cell depletion for cGvHD prevention is the use of *ex vivo* T cell depletion of the graft prior to HSCT. An early method of *ex vivo* TCD leveraged the ability of soybean lectin to induce differential agglutination of immune cells within the bone marrow product, allowing physical separation and removal of T cells and enabling HSCT from a haploidentical donor [87]. Another method of physical separation utilized counterflow centrifugation to separate lymphocytes by size and density [88]. With development of monoclonal antibodies, immunologic techniques were implemented to deplete T cells, for example, with OKT3 antibody [89], antibodies to CD6 [90,91], or cocktails of antibodies targeting T cells [92,93], all of which showed promise in small single center studies. Early studies have pointed to an increased risk of graft failure, infection, and most notably relapse in recipients of TCD for GvHD prophylaxis [94,95]. Subsequent studies have shown a clear increase in relapse risk associated with TCD for patients with CML [96,97]; however, the impact of TCD on relapse for AML is not well established [98]. An alternative ‘TCD’ strategy is to enrich for hematopoietic stem cells through CD34+ selection rather than T cell depletion *per se*. [99] This phase III prospective multicenter randomized trial compared CD34-selected peripheral blood stem cell HSCT (PBSCT) versus bone marrow HSCT (BMT) with PTCy alone for GvHD prophylaxis versus BMT with CNI/MTX as a control (conventional treatment) arm. Patients receiving CD34-selected PBSCT had a lower incidence of cGvHD but worse overall survival and treatment-related mortality with a higher incidence of death due to infections compared to the other arms, abrogating the benefit of reduced cGvHD [100]. More recently, specific depletion of naïve T cells has been employed in an effort to engineer the graft to preserve maximum GvL (presumably through administration of memory T cells) while reducing GvHD [101]. Grade III-IV acute GvHD was 7% while cGvHD was virtually nonexistent.

3.2. Ptcy

PTCy is a GvHD prophylaxis strategy wherein high-dose cyclophosphamide is administered in the days following HSCT. Initially employed as an approach to facilitate HLA haploidentical HSCT without excessive GvHD, the mechanism of action of PTCy may involve selective depletion of alloreactive T cells, while preserving regulatory T cells [102,103]. PTCy has markedly expanded the available HSCT donor pool by enabling haploidentical and HLA-mismatched transplants with acceptable rates of GvHD [104-109].

PTCy-based GvHD prophylaxis regimens have now been evaluated in several prospective randomized studies in the HLA-matched related and unrelated settings. The HOVON-96 trial demonstrated marked improvement in incidence of extensive cGvHD and in GvHD-free relapse-free survival (GRFS) in patients receiving PTCy with cyclosporine A (CsA) [110]. The BMT CTN 1203 trial studied a total of 273 patients who were randomized to receive either PTCy/tacrolimus/MMF), tacrolimus/methotrexate/bortezomib, or tacrolimus/methotrexate/maraviroc as GvHD prophylaxis after HSCT [111]. The primary composite outcome GvHD-free relapse-free survival (GRFS) pinpointed the PTCy/tacrolimus/MMF arm as having the most promising outcomes for subsequent direct comparison to tacrolimus/methotrexate and in larger phase III study. That subsequent study, BMT CTN 1703, has recently been reported [112]. Four hundred and thirty-one adult patients undergoing HSCT from a matched related or unrelated donor were evaluated. At one year, GRFS was 52.7% in the PTCy/tacrolimus/MMF group compared to 34.9% in the tacrolimus/methotrexate group with no differences in relapse rates or overall survival. Notably, BMT CTN 1301 showed that PTCy alone was insufficient for cGvHD reduction [100]. Rather, addition of CNI or a similar immunosuppressant appears to be necessary in combination with PTCy to achieve effective GvHD prophylaxis. These results will likely set a new standard of PTCy/tacrolimus/MMF for GvHD prophylaxis in the HLA-matched HSCT setting.

4. Strategies for treatment of cGvhd

4.1. Corticosteroids

Corticosteroids have long been employed for the treatment of both acute and cGvHD and remain first-line therapy [113,114]. While reasonably effective, long-term use is associated with significant adverse effects including infections, osteoporosis, and diabetes. Furthermore, up to half of patients ultimately become steroid resistant (SR-GvHD), and therapy options for SR-GvHD are limited [115-117]. Therefore, there is a need for alternative therapies that can reduce the dependence on corticosteroids.

4.2. Early experimental approaches

A number of therapies with initially promising results after smaller studies later failed to show benefit in larger randomized trials.

4.2.1. CNI—Corticosteroids combined with the CNI cyclosporin A (CsA) initially appeared to be effective for cGvHD treatment, but a randomized trial of 142 patients demonstrated no benefit with CsA addition [118,119].

4.2.2. Azathioprine—A small study suggested a benefit of addition of azathioprine to corticosteroids in preventing in cGvHD progression [120]; however, a subsequent large randomized trial could not replicate this finding [121].

4.2.3. Extracorporeal photopheresis (ECP)—ECP is a photodynamic therapy involving apheresis of lymphocytes followed by treatment with 8-methoxypsoralen and ultraviolet A (UVA), inducing a cytotoxic effect upon T cells [120,122]. Several small retrospective and prospective studies demonstrated responses of cGvHD to ECP, with some responses in the steroid-refractory setting (Table 1) [123-129]. Despite a paucity of randomized controlled evidence demonstrating a benefit for ECP, it is commonly employed, as it is considered safe and leads to improvement in quality-of-life measures for select patients with cGvHD.

4.2.4. Mycophenolate mofetil (MMF)—Some reports suggested that MMF could effectively mitigate symptoms in some patients with cGVHD (Table 1). In the upfront setting, however, MMF when added to steroids afforded no benefit and indeed there was a suggestion it may be detrimental compared to steroids alone [130-132].

4.2.5. Thalidomide—Thalidomide was recognized to have immunosuppressive effects in lepromatous leprosy [133], thus prompting interest in application to cGvHD. A prospective study of patients with refractory or high-risk cGvHD demonstrated responses in over half of patients [134]. Nevertheless, a subsequent randomized prospective trial failed to demonstrate response [135].

4.2.6. Sirolimus—Sirolimus (rapamycin), a mammalian target of rapamycin (mTOR) inhibitor is effective in combination with tacrolimus ± methotrexate for GvHD prevention during HSCT [136-138] and has antifibrotic properties in animal models [139]. A phase II/III randomized multicenter trial (BMT CTN 0801) aimed to evaluate the efficacy of sirolimus/prednisone versus sirolimus/CNI/prednisone for the treatment of cGvHD [140]. The study closed early due to a lack of statistical difference in the initial 138 evaluable patients.

4.2.7. Monoclonal antibodies—Several small studies suggested potential benefit of rituximab, a monoclonal antibody targeting B cells via CD20 [141-145]. Two small phase II studies of rituximab for steroid refractory cGvHD showed a 70-80% response rate (Table 1) [146,147]. Belimumab, a monoclonal antibody that targets BAFF, has been shown to reduce autoantibody production and improve skin symptoms in patients with cGvHD [148]. These promising results warrant further investigation; however, B cell depletion increases infectious risk in these already high-risk patients and should be used with caution [149].

4.3. Current landscape of approved therapies

4.3.1. Ibrutinib—Ibrutinib is an oral inhibitor of Bruton tyrosine kinase (BTK) (B cells) and IL-2-inducible T cell kinase (ITK) (Table 1, Figure 2) that has demonstrated efficacy in treating a variety of hematologic malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenström macroglobulinemia

(WM) [150,151]. More recently, ibrutinib has been evaluated as a potential therapy for cGvHD. Preclinical data suggested that BTK and ITK both play key roles in the development and maintenance of chronic inflammation, a hallmark of cGvHD. BTK/ITK inhibition with ibrutinib was shown to reduce inflammation and fibrosis in animal models of cGvHD [152]. Based on these promising preclinical results, several clinical trials of ibrutinib for the treatment of cGvHD were initiated.

Study PCYC-1129-CA was a multicenter, open-label, single-arm phase Ib/II study conducted to evaluate the efficacy and safety of ibrutinib in the treatment of cGvHD. The study enrolled 42 patients with cGvHD who had received at least one prior therapy. ORR was 67% at week 24, with 17% complete response (CR) and 50% partial response (PR). The median PFS was 12.7 months. Based on this study, ibrutinib was the first agent to gain FDA approval for next-line therapy for SR-GvHD [153,154]. Longer term follow-up demonstrated sustained response at 48 weeks in half of responding patients [155*]. Subsequent real-world experience with ibrutinib has been disappointing, with a single-center retrospective analysis demonstrating a 2-year failure-free survival rate (FFS) of 9% and median FFS of 4.5 months with no reduction in corticosteroid use with addition of ibrutinib [156].

4.3.2. Ruxolitinib—Ruxolitinib is a Janus kinase (JAK) 1/2 inhibitor that has been evaluated as a treatment for chronic graft-versus-host disease (cGvHD) in several clinical trials. JAKs play a key role in the pathophysiology of cGvHD by mediating the production of inflammatory cytokines and growth factors. Ruxolitinib has been shown to inhibit JAK-mediated signaling and reduce the production of pro-inflammatory cytokines and growth factors (Table 1, Figure 2). A preclinical model of ruxolitinib in a murine model of pulmonary cGvHD demonstrated reduced collagen deposition and improved pulmonary function testing [157].

A multicenter retrospective study evaluated outcomes after ruxolitinib treatment in patients with heavily pretreated steroid refractory cGvHD [158,159], Subsequently, a phase III randomized controlled trial of ruxolitinib for cGvHD trial (REACH3) enrolled 329 patients with steroid-refractory cGvHD [160**]. Patients were randomized to receive ruxolitinib at a dose of 10 mg twice daily or best available therapy (BAT). The study met its primary endpoint, with an overall response rate (CR + PR) of 49.7% in the ruxolitinib group compared to 25.6% in the BAT group ($p < 0.001$). The complete response rate was 7% in the ruxolitinib group compared to 0% in the BAT group. Treatment with ruxolitinib was associated with longer median failure free survival compared to BAT (>18.6 months versus 5.7 months, $p < 0.001$). The study concluded that ruxolitinib was effective in treating steroid-refractory cGvHD and represented a new standard of care for this patient population and led to both FDA approval and widespread adoption.

4.3.3. Belumosidil—Belumosudil is a small molecule inhibitor of Rho-associated coiled-coil containing protein kinase 2 (ROCK2), which is involved in regulating fibrosis and Th17/T regulatory cell differentiation via downregulation of IL321 and IL-17 via STAT3 (Table 1, Figure 2) [161]. ROCK2 plays an important role in the activation and migration of T cells, which are central to the pathogenesis of chronic graft-versus-host disease (cGvHD).

Preclinical models demonstrated reduced pulmonary and skin fibrosis with belumodudil treatment, suggesting a role for modulation of ROCK2 in the treatment of cGvHD [162].

The safety and efficacy of belumosudil in the treatment of cGvHD was evaluated in a phase IIa open label dose-finding study [163]. Patients were treated with one of the three different dose levels of belumosudil: 200 mg once daily, 200 mg twice daily, or 400 mg once daily, leading to overall response rates of 65%, 69%, and 62%, respectively. Median duration of response was 35 weeks with improvements in quality of life and corticosteroid dose reductions also observed for responding patients. Overall belumosudil was well-tolerated with no unexpected adverse events, no increased infectious risk, and low rates of cytopenias.

The subsequent ROCKstar trial confirmed efficacy with response rates ~ 75%. This study confirmed belumosudil as a promising therapy for cGvHD and contributed to the recent FDA approval of this drug for cGvHD after two or more lines of prior systemic therapy [164,165**].

4.4. Promising agents under active study

4.4.1. Axatilimab—Axatilimab is a novel humanized monoclonal antibody directed against colony-stimulating factor 1 receptor (CSF-1 R) that is currently under study for the treatment of cGvHD. Colony stimulating factor 1 (CSF-1) directs differentiation and proliferation of pro-fibrotic macrophages, promoting tissue remodeling, a key component of the pathogenesis of cGvHD (Figure 2) [166]. Preclinical studies in mice demonstrated that development of cGvHD-like pathology in the skin was dependent upon macrophage infiltration driven by CSF-1/CSF-1 R. On this basis, axatilimab was developed to recognize and bind the ligand-binding domain on CSF-1 R to block binding of CSF-1, leading to inhibition of monocyte activation.

To test this in humans, a phase I/II study evaluated the safety and tolerability of axatilimab in 40 patients with recurrent cGvHD [167,168**]. Overall response at cycle 7 day 1 was 50% in the phase II cohort (11 of 22 patients). A second randomized multicenter phase II trial testing three different dose levels of axatilimab in patients with recurrent or refractory cGvHD after at least 2 lines of prior systemic therapy is currently underway (AGAVE-201) (Table 1) [169].

4.4.2. Abatacept—Abatacept is a first-in-class recombinant soluble fusion protein selective modulator of T cell costimulation composed of the Fc region of immunoglobulin IgG1 fused to the CTLA-4 extracellular domain. It functions by binding to the B7 domain on antigen presenting cells, preventing effective delivery of costimulation during antigen presentation to T cells and attenuating T cell stimulation (Figure 2) [170]. Based on its success in treating rheumatologic diseases [171] and promising preclinical studies showing amelioration of cGvHD pathology in mice [172], abatacept was trialed for prevention and treatment of GvHD in humans. Abatacept recently gained FDA approval for prevention of acute GvHD after the GvHD-1 trial, a randomized placebo-controlled study, demonstrated improved rate of acute GvHD without a negative impact on relapse or infectious complications [73]. A phase I trial to evaluate safety, efficacy, and immunologic modulation in patients with steroid refractory cGvHD treated with abatacept at escalating

doses demonstrated a 44% partial response rate (Table 1) [173]. Abatacept treatment was associated with increased PD-1 expression on circulating CD4+ and CD8+ T cells from responders, suggesting that abatacept promotes T cell exhaustion, thereby mitigating cGvHD. Recently, a phase II study evaluating efficacy of abatacept in the treatment of steroid refractory cGvHD has been published, confirming phase I results [174]. Overall, these studies suggest that abatacept may be an effective and well-tolerated treatment option for patients with cGvHD who are refractory to steroids.

4.4.3. Low dose IL-2—Interleukin-2 (IL-2) is a key cytokine that regulates T cell homeostasis, activation, and differentiation [175]. Regulatory T cells (Tregs) are particularly dependent upon IL-2 signaling from activated T cells for maintaining their suppressor function [176-178]. This dependence has been exploited for therapy in autoimmune disorders by treatment with low-dose IL-2 in an effort to restore Treg fitness and function, thereby modulating inflammation [179]. Since cGvHD is associated with a loss of tolerance and impaired Treg function [45,180,181], IL-2 was hypothesized to mitigate cGvHD in humans, through immunomodulation of Treg survival and function [182]. A phase I dose-escalation study demonstrated the tolerability of IL-2 in patients with active steroid refractory cGvHD, with half of patients having a response (Table 1) [183]. Patients had increased numbers of CD4+ T reg cells as well as an increased ratio of Treg to conventional CD4+ T cells (Tcon). Correlative analysis showed increased Treg proliferation, thymic export, and enhanced resistance to apoptosis with minimal changes in Tcon cells, suggesting a mechanism by which IL-2 promotes immune tolerance [184].

5. Biological insights into GvL

GvHD and GvL have long been thought to be two sides of the coin in transplant immunology, inextricably linked to one another. Indeed, the seminal work by Horowitz and colleagues recognizing the GvL effect of HSCT tied this phenomenon to the development of cGvHD [16]. However, randomized trials in the modern era showing improved GvHD prophylaxis, including BMT CTN 1703 (PTCy), have not resulted in increased relapse risk even despite substantial improvement in cGvHD. Thus, modern biological insights suggest that GvL and GvHD, while closely related, may be separable. Therefore, therapies to enhance GvL without increasing cGvHD present an attractive option for improving outcomes. The molecular underpinnings driving the GvL effect after HSCT have garnered much attention with many potential cell subsets and mechanisms implicated. Yet, successful translation of these findings to clinical application of influencing GvL remains elusive.

5.1. T cells

T cells have long been hypothesized as the primary driver of the GvL effect, a notion supported by the success of donor lymphocyte infusions (DLI) [185-193] and tapering of immune suppression [14] in reinducing remissions for patients with relapsed disease or dropping donor chimerism. Multiple potential T cell subsets and putative mechanisms of effective GvL have been proposed. Since T cell therapies for CML demonstrate the most clinically effective GvL response, several studies have utilized this disease setting as a model to understand T cell mechanisms underlying this effect. One study in mice with retrovirally

transduced bcr-abl fusion cDNA demonstrated both CD4 and CD8 T cell-mediated GvL in a Fas/FasL-independent mechanism [194]. A more recent study identified the expansion of precursor exhausted T cells defined response following DLI [195,196]. Intriguingly, this study suggested that the expanding cells thought to be mediating GvL response to DLI originated from the bone marrow microenvironment, rather than from the DLI product itself, suggesting a T helper function of DLI in CML as opposed to direct cytotoxicity, a notion that has received support from mouse models of GvL [197,198].

Whether GvL is mediated through antigen-specific or antigen-independent T cell activity remains an open question. Classes of potential antigens include leukemia-associated antigens (LAAs), leukemia neoantigens, and minor histocompatibility antigens (mHags) [199]. Multiple potential LAAs have been identified with evidence supporting the idea that these LAAs are capable of inducing T cell activation and cytotoxicity. One of the best described potential LAAs is Wilms' tumor 1 (WT1), a common tumor marker expressed by some CD34+ leukemia cells [200], and multiple studies have demonstrated WT1-specific T cell cytotoxicity capable of eliminating leukemia cells utilizing vaccination strategies, bispecific antibodies, and adoptive cellular transfer [201-213]. Other antigens that have been studies as potential LAAs for inducing T cell cytotoxicity include Cancer-testis antigen (CTA) Preferentially-expressed Antigen in Melanoma (PRAME), Survivin, and CTA New York Esophageal Squamous Cell Carcinoma −1 (NY-ESO-1) [214-217]. Efforts to better characterize and engineer LAA-specific T cells with the hope of improving antigen specificity of adoptive cellular therapy while limiting toxicities including GvHD [218-224].

Minor histocompatibility antigens provide an attractive alternative to LAAs for harnessing donor T cell alloreactivity [225,226]. While LAAs may not be present on all leukemia cells, nearly all donor-recipient pairs will have some mHag mismatch due to genetic polymorphism, although relative immunogenicity of different mhAgs varies [227-229]. Given the large number of potential mHags, several high throughput efforts to identify mHags with putative GvL activity, as well as to identify those that may increase risk for GvHD [230-235]. Candidate mHags and mHag-reactive T cells have shown potential for memory generation and reactivity in support of a role in effective GvL in both animal models and humans [236-242]. In particular, Y chromosome genes have shown promise in inducing T cell reactivity in sex-mismatched transplantation, particularly given the relationship between Y-antigen alloantibodies and development of GvHD [236-240,243].

In addition to LAAs and mHags, viral antigens may also prime anti-leukemic T cell activity; however, the extent of cross reactivity is unclear [244-246]. Some studies have demonstrated successful reprogramming of virus-specific T cells toward mHags by transfer of TCR, leading to dual specificity of these T cells to both virus and mHag [245]. A phase I study of these reprogrammed cells in 5 patients with AML showed that cells can be safely infused but feasibility and efficacy was limited [247].

Vaccination strategies have been attempted to capitalize upon T cell alloreactivity in the absence of known leukemia antigens. One such strategy, GVAX, utilized vaccination with irradiated, adenovirus transduced autologous myeloblasts early after HSCT in an attempt to induce leukemia-specific donor alloreactivity; however, this study did not show an

improvement in survival for patients with myelodysplastic syndrome (MDS) or AML [248]. Another recent vaccination strategy involved creation of 'hybridomas' derived from fusion of patient AML cells with autologous dendritic cells (DC), aimed at improving antigen presentation in the context of DC co-stimulation to prime antigen-specific donor T cell alloreactivity [249]. Though the study was small, the response rates were highly encouraging, and analysis of patient T cells demonstrated post-vaccination tumor-specific activity, durable at least six months following vaccination.

Aside from the identification and targeting of specific antigens for enhancing GvL, the success of T cell exhaustion reversal in solid tumors using immune checkpoint blockade (ICB) in recent years has sparked interest in the application of these therapies to enhance GvL. Indeed, models of GvL support this notion, given that mHAg-specific T cells become progressively more exhausted, with expression of TOX and inhibitory receptors and decreased expression of interferon (IFN)-ɣ, upon chronic mHag exposure, with reversal of exhaustion seen after PD-1 blockade [250]. Studies in mice supported the notion that PD-L1 blockade effectively reverses exhaustion of alloreactive CD8 T cells and restores effective GvL [251]. A phase I study in humans demonstrated success of CTLA-4 blockade with ipilimumab in reducing disease burden in patients with post-HSCT relapsed myeloid malignancy [252]. Characterization of biopsy specimens in responders revealed enhanced infiltration of CD8 cytotoxic T cells, suggesting reversal of T cell exhaustion and reinvigoration of effective CD8 T cell-mediated GvL [253]. In further support for the role of T cell exhaustion, high expression of TIGIT on CD4 T cells has been associated with higher risk of AML relapse [254]. Mouse models of AML and myeloma have shown effective generation of GvL after depletion of exhausted CD8 T cells, further underscoring the key role of T cell exhaustion in GvL [255]. Nevertheless, the role of T cell exhaustion in mediating a balance between GvL and GvHD requires further investigation, as case reports of ICB in patients with AML have resulted in severe GvHD and other inflammatory cascades such as secondary hemophagocytic syndrome (sHLH) [12,256].

5.2. Inflammatory cytokines and interleukins

Cascades of inflammatory cytokines produced by T cells can stimulate cytokine and interleukin production from myeloid and other lymphoid cells, which under certain circumstances can lead to GvHD, but if correctly tuned may enhance GvL. An early effort to identify soluble effector molecules with separable GvHD and GvL activity demonstrated that human interleukin (IL)-11 could selectively inhibit GvHD mediated by CD4 T cells but did not inhibit GvL activity in CD4 or CD8 T cells [257]. Similarly, injection of IL-12 has been shown in mice to prevent GvHD without impairing GvL activity [258-260]. Subsequent work demonstrated that IL-12 production by plasmacytoid dendritic cells in bone marrow grafts mediated effective GvL activity [261]. IL-18 has also been shown to ameliorate GvHD while preserving GvL [262,263].

The SORMAIN study demonstrated improvement in outcomes for patients with AML with internal tandem duplication mutations in the *FMS*-like tyrosine kinase 3 gene (*FLT3*-ITD) treated with the tyrosine kinase inhibitor sorafenib [264]. Correlative studies have subsequently demonstrated an increase in production of IL-15 in patients responding to

sorafenib treatment, raising a possible mechanism of response and a potential avenue for therapeutic exploitation in other AML treatment settings [265]. Indeed, other studies have implicated IL-15 as a possible stimulator of GvL activity for AML due to its ability to activate T and NK cells through the IL-2/15RRβγc receptor [265]. A phase I first-in-human study of recombinant IL-15 for patients with relapsed leukemia/lymphoma after HSCT, which showed activation and proliferation of NK and CD8+ T cells after treatment [266].

Interferon (IFN)-ɣ is a key inflammatory cytokine secreted by both T cells and innate immune cells with implications in both GvL activity and GvHD pathogenesis after HSCT [267,268]. AML cells exposed to IFN-ɣ are sensitized to direct T cell cytotoxicity [269]. Further, mature dendritic cells derived from AML blasts are able to stimulate T and NK cells to promote IFN-ɣ and cytotoxicity [270]. Type I interferons are also important for sensitizing leukemia cells to T cell cytotoxicity and for promoting T cell cytotoxic function [271]. Intriguingly, a phase I trial leveraging IFN-ɣ treatment to augment GvL responses of DLI has recently been reported [272]. IFN-ɣ was injected subcutaneously into four patients with relapsed MDS/AML, followed by administration of DLI. Three patients subsequently achieved remission, suggesting IFN-ɣ therapy as a promising adjunct for promoting T cell alloreactivity with subsequent DLI.

5.3. NK cells

NK cells are innate lymphoid cells imbued with natural cytotoxicity [273]. NK cells are prevented from killing healthy autologous cells by inhibitory signals mediated through the ligation of the nonclassical MHC class I molecular human leukocyte antigen (HLA)-E and an NK-cell heterodimer consisting of CD94-NKG2A [274-276]. NK cells exert their effector function through ligand recognition by molecules such as killer-cell immunoglobulin-like receptors (KIR) which recognize HLA molecules on target cells (e.g. virally infected cells or tumor cells) [277]. Analogous to MHC mismatch leading to T cell alloreactivity, mismatches in KIR epitopes are a well-established mechanism of NK cell alloreactivity, leading to NK cell mediated killing of mismatched cells [278-283]. KIR-mismatched HSCT has been evaluated for potential for enhanced NK cell-mediated alloreactivity. One study of 60 patients, 20 of whom harbored donor-recipient KIR mismatch, demonstrated that donor NK cells were capable of direct cytotoxicity against recipient leukemia cells [284]. Multiple subsequent studies have supported the notion that KIR mismatch reduces relapse risk after HSCT and is associated with enhanced NK cell expansion, possibly promoting more effective GvL [285-291]; however, a recent large retrospective registry study found no link between KIR mismatch and protection from relapse [292]. Nevertheless, there is considerable interest in leveraging NK cell/KIR biology to develop novel NK-cell-based therapies for hematologic malignancies [293,294].

In addition to KIR mismatch-mediated NK alloreactivity, other subsets of NK cells with specific anti-tumor activity have recently been identified and are under active investigation as novel therapeutics. Initial efforts at specific transfer of allogeneic NK cells have been limited by inadequate persistence and GvL activity [295,296]. However, activation of memory-like NK cells with a cytokine cocktail of IL-12, IL-15, and IL-18 (CIML-NK cells) was demonstrated in mice to have improved persistence and activity against AML blasts

[297-300]. A phase I trial using these CIML-NK cells in patients with relapsed myeloid malignancy after haploidentical HSCT demonstrated expansion, activation, and long-term persistence of these cells [301]. Preclinical studies have recently leveraged these CIML-NK cells along with a chimeric antigen receptor (CAR) targeting nucleophosphmin-1 (NPM1) [302]. Further studies are needed to advance our understanding of NK cell GvL biology.

5.4. Additional potential mediators of GvL

Preclinical and animal studies have identified other potential modulators of GvL. For example, non-coding RNAs that control gene expression have been shown to fine-tune cellular responses including cytotoxicity and to regulate T cell responses after HSCT [303]. Multiple potential metabolic targets for modulating T cell alloreactivity have been posited, including the inhibition of HMG-CoA reductase, which protects from GvHD while preserving GvL in mice [304]. Similarly, high levels of lactic acid inhibit T cell proliferation, while treatment with sodium bicarbonate to reduce lactic acid-induced low intracellular pH enhances T cell reactivity in both mice and human cells [305]. Vasoactive intestinal peptide (VIP) is a neuropeptide with a role in regulation of inhibitory pathways in immune cells including T and NK cells. Agonism of VIP signaling induces T cell proliferation and reduces regulatory IL-10 expression, leading to enhanced GvL activity in animal models, suggesting a novel pathway for tuning T cell activity [306]. Autophagy induction in donor T cells can promote GvHD, while inhibition of autophagy leads to increased cytokine production and cytotoxicity through reduced degradation of intracellular cytotoxic enzymes leading to improved GvL activity [307]. Various transcription factors and epigenetic modifiers have also been implicated in tuning T cell function. The transcription factor promyelocytic leukemia zinc finger (PLZF) attenuates effector function in alloreactive T cells, thereby reducing GvHD but preserving GvL effects [308]. The polycomb repressive complex 2 (PRC2) has been shown to drive immune escape pathways in AML through repression of MHC II expression in leukemia cells, while inhibition of PRC2 preserves MHC II expression promoting GvL activity by CD4 T cells [309]. Similarly, inhibition of mouse-double-minute-2 (MDM2) in patient derived AML xenograft models induces both MHC I and II expression in AML cells, leading to improved apoptosis through TRAILR1/2 [310].

6. Conclusions and future outlook

GvHD and GvL are complex immunological phenomena unique to patients after allogeneic HSCT. Understanding the specific mechanisms driving GvHD and GvL are critical for the development of effective therapies targeting these pathways. While the field has made substantial progress in recent years toward understanding the biology of cGvHD and developing novel strategies for prevention and treatment, little progress has been made toward leveraging GvL for improvement in relapse. Early evidence suggested close linkage of GvL with cGvHD, and indeed, for CML this appears to be true since TCD abrogates GvL and increases relapse risk. However, in the modern era, CML is an infrequent indication for HSCT, and in other diseases such as MDS and AML, currently the most frequent indication for HSCT, GvL and cGvHD appear to be separable. Recent developments in strategies for reducing (e.g. PTCy) and treating (e.g. ruxolitinib) cGvHD have not

led to higher rates of relapse. Some retrospective studies have raised the possibility of increased relapse risk using PTCy, though this has not borne out in randomized trials [110,112,311,312]. Thus, future experimental approaches for augmenting GvL are likely to be obtainable without exacerbating cGvHD, though these are yet undefined. The mechanisms contributing to effective GvL are likely multifactorial; indeed, the multitude of published literature establishing potential mediators of GvL *in vitro* and in animal models underscores the challenge of uniting transplant immunobiology into a cohesive and comprehensive understanding of GvL activity. Thus, there is ample opportunity for progress in understanding and promoting this phenomenon toward improved treatments to enhance outcomes.

7. Expert opinion

Chronic graft versus host disease (GvHD) has historically been an understudied complication of allogeneic hematopoietic stem cell transplantation (HSCT), with other challenges including relapse, infection, and treatment of acute GvHD taking precedence due to their impact on morbidity and mortality in the early years after HSCT. Furthermore, clinical manifestations of cGvHD are protean and often a diagnosis of exclusion, rendering rigorous study of the pathophysiology difficult. The advent of improved therapies for hematologic malignancies has led to longer-term survival for a greater number of patients after HSCT. Further, expanded access to HSCT through greater availability of alternative donors including HLA-mismatched and haploidentical donors not only increases the cumulative incidence of cGvHD but also increases the individual risk in these patients of developing cGvHD because of greater HLA-disparity. Other recent changes in standard practice of HSCT, including a shift toward using peripheral blood stem cells (PBSCs) rather than bone marrow grafts, have also resulted in greater incidence of cGvHD. While historically options for prevention and treatment of cGvHD have been limited, recent years have seen renewed interest in discovery of underlying mechanisms of cGvHD as well as several new therapies gaining approval for treatment, particularly in the steroid-refractory setting, including recent FDA approvals for ibrutinib, ruxolitinib, and belumosudil. Curiously, these treatments act through different biological pathways, underscoring both the multifactorial nature of the disease as well as the fact that current knowledge about the molecular underpinnings of this process remains in its infancy.

GvL, on the other hand, is an immunological phenomenon favorable after HSCT wherein donor immune cells recognize and eliminate residual malignant cells from the recipient, preventing recurrence and maintaining remission. For decades, whether GvHD are inherently intertwined has been a subject of debate. However, recent strategies for better cGvHD prevention (e.g. PTCy) and several new approved medication for cGvHD treatment (ruxolitinib, belumosudil, ibruitinib) have not led to increased rates of relapse, indicating the ability to separate these immunologic phenomena. Thus, while they are clearly closely related, the opportunity exists to separate cGvHD and GvL and thereby enhance the latter without inflaming the former. A mechanistic definition of GvL is lacking despite long standing clinical demonstration of this phenomenon. Improved basic biological understanding of both these immunological sequelae of HSCT are needed for development of better clinical strategies to promote GvL and reduce GvHD.

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Article highlights

- Nearly half of patients may relapse with their original disease and is the major cause of mortality after HSCT. Chronic graft versus host disease (cGvHD) is a leading contributor to morbidity in long-term survivors after HSCT
- GvL and cGvHD are closely-related immunologic phenomena after HSCT both likely dependent upon activity of alloreactive donor immune cell subsets, though the precise mechanisms driving both are likely multifactorial and poorly defined
- Although there have been recent advances in strategies for prevention and treatment of cGvHD, there is an urgent need for improved understanding of GvL

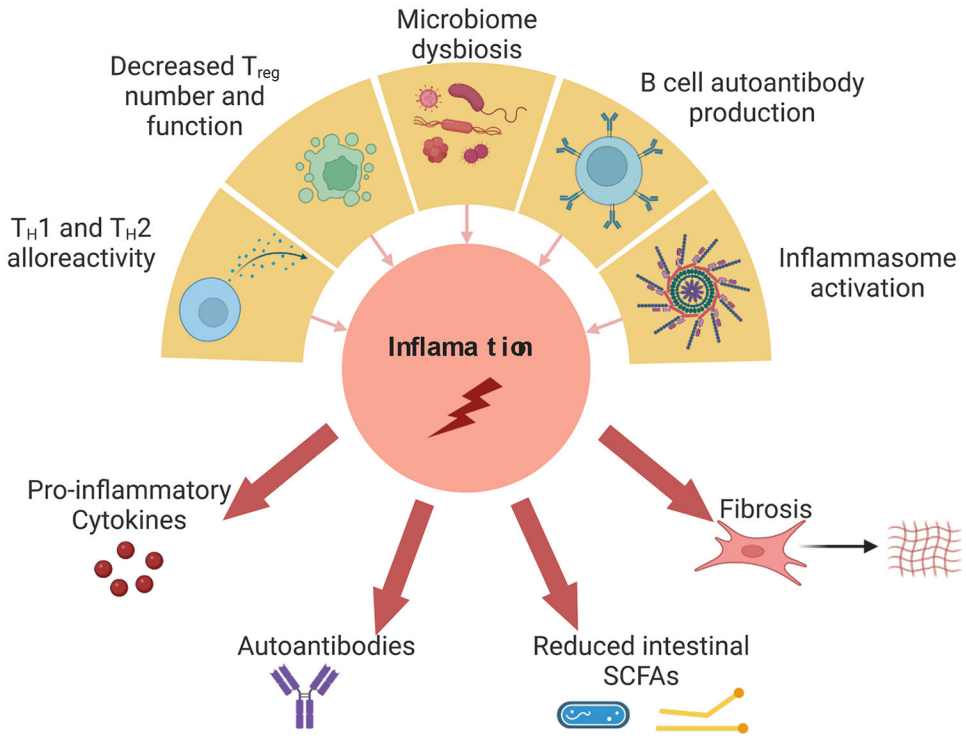

Figure 1.

Depiction of example cell types and factors leading to increased likelihood of cGvhd (top) which mediate inflammation through a variety of mechanisms including pro-inflammatory cytokine production, autoantibody production, and development of fibrosis (bottom).

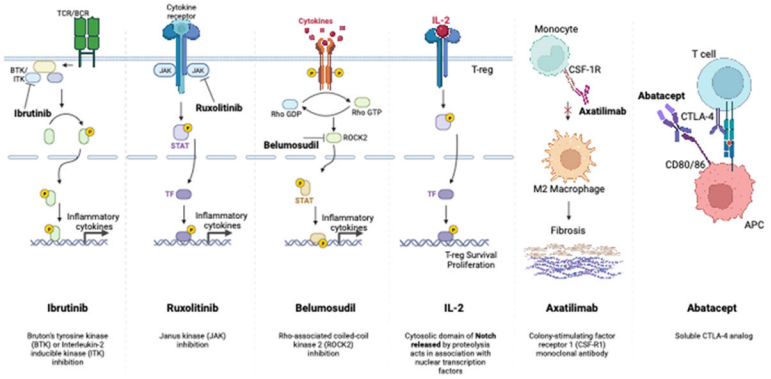

Figure 2.

Summary of the mechanisms of action of three currently FDA approved treatments for cGvhd (ibrutinib, ruxolitinib, belumosudil) as well as three experimental agents currently under investigation (IL-2, axatilimab, abatacept).

Table 1.

Agents for treatment of cGvHD and their proposed mechanisms of action.

Agent	Type of Molecule	Molecular Target	Proposed Mechanism	Response Rate	Citation(s)
Ibrutinib	Small Molecule Inhibitor	BTK/ITK	Inhibition of B and T cell activation and differentiation	12–69%	• Miklos et al. [153,154] • Waller et al. [155] • Chin et al. [156]
Ruxolitinib	Small Molecule Inhibitor	JAK1/2	Reduced T effector cell proliferation	50–82%	• Zeiser et al. [157] • Zeiser et al. [158] • White et al. [159]
Belumosudil	Small Molecule Inhibitor	ROCK2	STAT3 phosphorylation; decrease in Th17/Treg ratio	62–75%	• Flynn et al. [162] • Jagasia et al. [163] • Cutler et al. [165] • Zanin-Zhorov et al. [161]
ECP	-	Lymphocytes	T cell cytotoxicity through sensitization to UVA	8–69%	• Greinix et al. [124] • Flowers et al. [125] • Greinix et al. [126] • Couriel et al. [129]
Rituximab	Monoclonal Antibody	CD20	Inhibition of antibody production	65–86%	• Zaja et al. [141] • Cutler et al. [146] • Kim et al. [147]
MMF	Enzyme Inhibitor	IMP Dehydrogenase	Inhibition of T and B cell proliferation	23–62%	• Krejci et al. [130] • Furlong et al. [131] • Martin et al. [132]
Axatilimab	Monoclonal Antibody	CSF-1 R	Inhibits monocyte activation, preventing fibrosis	50%	• Alexander et al. [166] • Kitko et al. [167] • Lee et al. [168]
Abatacept	Fusion Protein – CTLA-4	CD80/CD86	Prevents T cell co-stimulation	44–58%	• Nahas et al. [173]

Agent	Type of Molecule	Molecular Target	Proposed Mechanism	Response Rate	Citation(s)
				•	Koshy et al. [174]
Low dose IL-2	Recombinant Cytokine	T cells/Tregs	Improves Treg fitness and function	50%	• Koreth et al. [183]
					• Matsuoka et al. [184]