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Through the Pharmacists' Lens:
A Deep Dive into the Practice Dynamics in Graft-versus-Host Disease

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Introduction

GVHD disease state

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is a potentially curative therapeutic option that has been used in hematology practice for more than 5 decades for patients with malignant and nonmalignant hematologic conditions, as well as some autoimmune diseases.[1,2] Of note, for hematologic malignancies, allo-HSCT is considered the first true cancer immunotherapy, well before the advent of checkpoint inhibitors and other cellular immunomodulatory therapies (such as chimeric antigen receptor T-cell therapies).[3] The use of allo-HSCT has increased over time, in part due to the expansion of indications for HSCT, and the increasing benefit/risk ratio for this modality with the progressively broader use of reduced-intensity conditioning regimens over time along with improvements in anti-infectious therapies. These advances decreased early transplant-related mortality (TRM)[1] and have led to the application of allo-HSCT in patients with advanced age (>60 years) and/or less than optimally "fit."[4] However, TRM is a persistent challenge due to allo-HSCT–associated complications.[5,6]

Graft-versus-host disease (GVHD) is a common, predominant, and formidable systemic complication occurring after allo-HSCT that can result in TRM, as well as significant morbidity.[6-9] It was first described in 1959 by Billingham and Bernt following splenic-cell transplantation as a "runt disease" leading to thinning, loss of skin elasticity with erythema, areas of exfoliation, and cessation of weight gain.[10] Three conditions were described as being necessary for development of GVHD—graft must contain immunocompetent cells, the host must contain allo-antigens that can be recognized by immunocompetent cells of the graft, and the host must be unable to mount an appropriate immune response against the graft.[10] GVHD occurs in ≤50% of allo-HSCT recipients from human leukocyte antigen (HLA)-matched donors and at higher rates with unmatched donors.[8] In one analysis, the cumulative incidence of GVHD after reduced-intensity conditioning allo-HSCT was 66% at 10 years post-transplant; these data underscore the persistence of high incidence and associated clinical sequelae of GVHD in transplant recipients, leading to a significant morbidity burden.[6] Moreover, GVHD is a major cause of mortality, with more than 10% of allo-HSCT patients dying from this complication.[8] Indeed, GVHD is second only to disease relapse as the cause of mortality following HSCT.[8,11]

> GVHD is a common, predominant, and formidable systemic complication occurring after allo-HSCT that can result in TRM, as well as significant morbidity.

The standard classification of GVHD as a disease process is based on the timing of its presentation as per the National Institutes of Health (NIH) Chronic GVHD Consensus projects—acute GVHD (aGVHD) occurring within 100 days post-transplant and chronic GVHD (cGVHD) being defined as symptom appearance or persistence after the 100-day post-transplant cutoff.[8] With the 2014 updated NIH classification based on clinical manifestations, these categories have been further subdivided into 4 types—classic aGVHD; persistent, recurrent, or late-onset aGVHD; classic cGVHD; and overlap syndrome (**Figure 1**).[11,12]

Although potentially lethal, aGVHD typically runs a limit-

Figure 1. Classification of GVHD and Manifestations

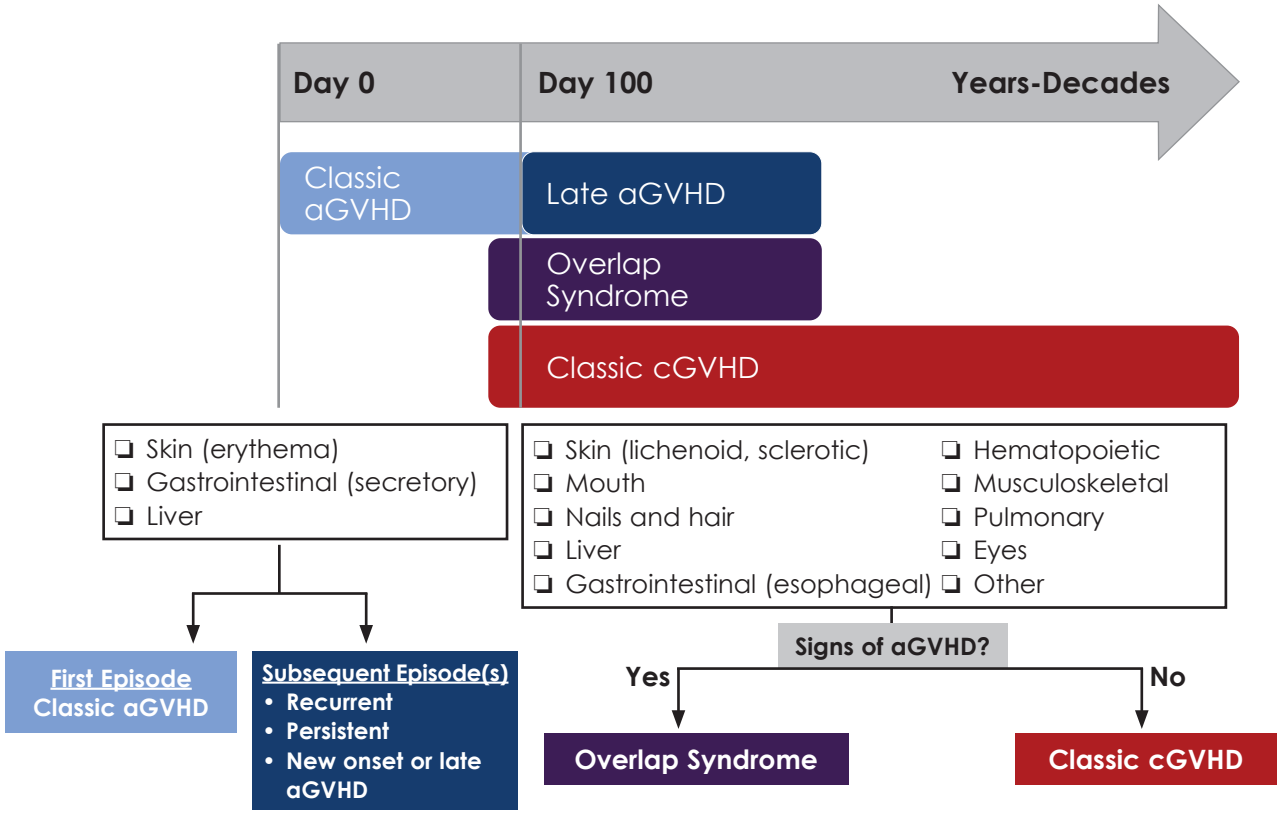


Figure recreated based on Figure 1 in Mawardi et al, 2019.[11]
aGVHD indicates acute graft-versus-host-disease; cGVHD, chronic graft-versus-host disease; GVHD, graft-versus-host disease.

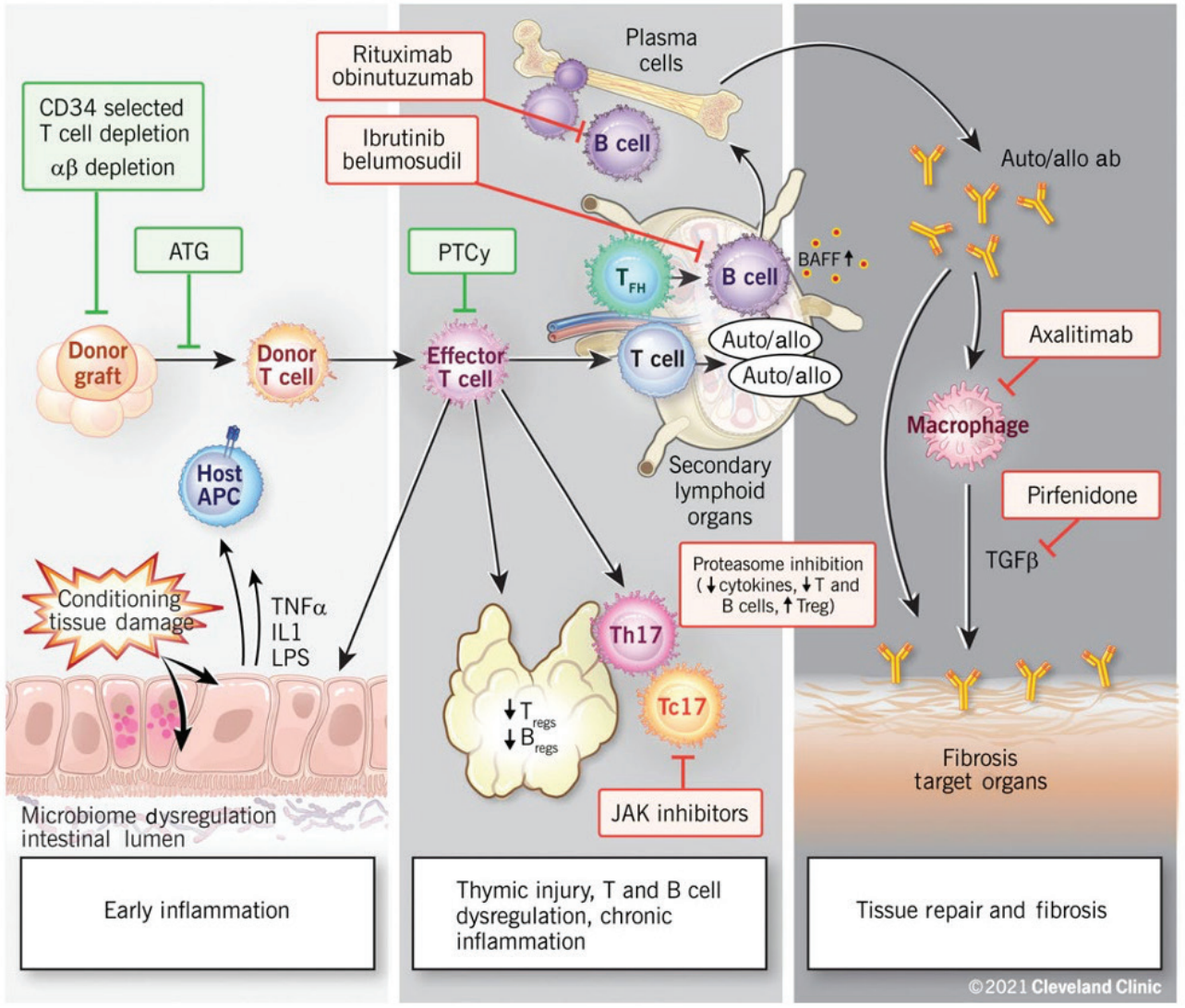
ed course, whereas cGVHD can be active for many years, even decades, potentially requiring prolonged management with immunosuppressive therapies.[11] cGVHD is also associated with significant risk of long-term complications and morbidity, related to both the natural evolution of the GVHD process itself as well as iatrogenic toxicities from the various therapies used for its management.[11] The NIH diagnostic criteria provide a standardized framework for recognition of cGVHD and disease severity, in addition to improving clinical trial design and implementation in the GVHD space;[12] however, many patients do not meet NIH diagnostic criteria until irreversible manifestations of GVHD have already developed.[13] To address these challenges, the NIH convened working groups in 2020 to draft further guidance on early recognition of cGVHD (discussed in **"Management of GVHD"**).[13,14]

GVHD disease state

Although GVHD is considered a rare disorder,[15] approximately 35% to 50% of patients with hematologic malignancies will develop GVHD after allo-HSCT, making it a common and often devastating HSCT-associated complication.[2,16] More than 23,000 HSCTs were performed in the United States alone in 2019; moreover, the number of HSCTs is expected to increase over time with expanding indications and a more aggressive therapeutic approach nowadays, especially for patients with hematologic malignancies.[16,17] Given the anticipated increase in HSCT use in clinical practice, GVHD represents a substantial and continuing challenge. While aGVHD can occur in ≤50% of HSCT recipients from HLA-matched sibling donors, with higher prevalence in recipients from unmatched donors, the incidence of cGVHD varies from 6% to 80%, depending on the HSCT source, donor type, and the exact nature and intensity of post-HSCT immunosuppressive therapy.[11] The projected prevalence of cGVHD in the United States in 2016 was 14,017 individual patients, with 42% of patients developing cGVHD within 3 years post-transplant and a prior diagnosis of aGVHD reported in 66% of cases.[18]

Although some studies report the reduction of cGVHD prevalence to 10% to 15% with the introduction of T-cell depletion–/post-transplant cyclophosphamide–mediated preventive approaches,[19-21] the estimated incidence of cGVHD is 30% to 50% in transplant recipients of allogeneic peripher-

Figure 2. Proposed Biologic Phases of cGVHD and Associated Molecular Targets



Adapted from Hamilton, 2021.[46] Complex and dynamic processes promote cGVHD development in 3 biologic phases characterized by: early inflammation; thymic injury, T- and B-cell dysregulation, and chronic inflammation; and aberrant tissue repair and fibrosis. In phase 1 (left panel), host tissue damage begins during pretransplant conditioning, resulting in release of inflammatory cytokines, which activate donor allo-reactive T-cells and promote differentiation and expansion of effector T-cells. Gut tissue damage and the resulting release of gut microbial contents activates. Ex vivo CD34+-selected T-cell depletion and ATG are phase 1–directed strategies for reducing GVHD risk. In phase 2 (center panel), thymic injury enables auto- and all-reactive T-cells to emerge and propagate. Moreover, loss of central and peripheral tolerance leads to dysregulation of Tregs and B-cells. Expansion of donor Tfh cells in the secondary lymphoid organs promotes the survival, expansion, and differentiation of donor B-cells into aberrant anti-host immunoglobulin-producing plasma cells. Therapeutic strategies aimed at the second phase of GVHD include PTCγ, proteasome inhibitors, JAK inhibitors, and B-cell–directed agents (ibrutinib and belumosudil; CD20-targeted rituximab and obinutuzumab). The third phase is characterized by aberrant repair of tissue via excessive ECM accumulation and subsequent fibrosis. The mAb axalitimab and the oral antifibrotic agent pirfenidone are therapeutic approaches that target the third phase.
APC indicates antigen-presenting cell; ATG, anti-thymocyte globulin; BAFF, B-cell activating factor cGVHD, chronic graft-versus-host disease; ECM, extracellular matrix; GVHD, graft-versus-host disease; IL1, interleukin 1; JAK, Janus kinase; LPS, lipopolysaccharide; mAb, monoclonal antibody; PTCγ, post-transplantation cyclophosphamide gamma; Tfh, T follicular helper; TNFα, tumor necrosis factor alpha; Treg, regulatory T-cell.

al-blood stem-cell grafts even with GVHD prophylaxis.[13] cGVHD risk factors include a prior episode of aGVHD, receipt of peripheral-blood stem-cell grafts, gender mismatch between donor and recipient, HLA disparity between recipient and donor, older age of the recipient or donor, and a diagnosis of chronic myeloid leukemia.[9] The symptom/disease, healthcare resource, and societal burden of GVHD is substantial, due to the broad and profound impact of GVHD on long-term health status outcomes such as health-related quality of life, social/productivity costs, and healthcare utilization

Table 1. Clinical Features of aGVHD and cGVHD

Organ/System	aGVHD	cGVHD
Skin	Maculopapular rash	Depigmentation, poikiloderma, scleroderma-like features
Liver	Cholestatic hyperbilirubinemia	Jaundice, elevated LFTs
Upper GI tract	Nausea, anorexia	Anorexia, weight loss, esophageal web, or strictures
Lower GI tract	Diarrhea (often bloody), severe abdominal pain	
Mouth	Ulcerative and erythematous changes diffusely, lip crusting	Xerostomia, lichen planus–like features, sicca syndrome–like features, trismus, mucoceles
Nails	N/A	Nail dystrophy, longitudinal ridging, onycholysis
Eyes	N/A	Dry eyes, sicca syndrome, conjunctivitis, panuveitis
Muscle, fascia, joints	N/A	Myositis, fasciitis, joint stiffness
Female genitalia	N/A	Vaginal sclerosis/stenosis, ulceration, lichen planus–like features
Male genitalia	N/A	Lichen planus–like features, phimosis, scarring/stenosis
Lungs	N/A	Pleural effusion, bronchiolitis obliterans, obstructive pulmonary disease
Kidneys	N/A	Nephrotic syndrome
Heart	N/A	Pericarditis

Table adapted from Mawardi et al, 2019.[11]
aGVHD indicates acute graft-versus-host-disease; cGVHD, chronic graft-versus-host disease; GI, gastrointestinal; LFTs, liver function tests; N/A, not applicable.

Table 2. Summary of Baseline Assessments Pre-Transplant and Day +100 Post-Transplant

Organ System	Required Clinical Documentation
Skin (including nails and hair)	Baseline skin abnormalities (scars, vitiligo, etc) with photo-documentation, if possible
Mouth	Presence of linea alba, lichen planus–like changes, and mucosal
Eye	Presence of dry eyes and other eye symptoms, use of prescribed or over-the-counter eye drops
Lung	Pulmonary function tests including spirometry (FEV_1, FVC, ratio, $FEF_{25\%-75\%}$), lung volumes (VC, TLC, RV), and DLCO*
Liver	Bilirubin, AST, ALT, alkaline phosphatase
GI tract	Presence of anorexia, nausea, vomiting, diarrhea, dysphagia, and food allergies/intolerance
Fascia/joints	Baseline limb mobility issues and P-ROM For the pediatric adaption of P-ROM, see EBMT handbook[60]
Genitalia	Evidence of lichen planus–like lesions, erythema, ulcers, fibrosis, or phimosis in males (ideally, women will be evaluated by a gynecologist)

Table adapted from Kitko et al, 2021.[13]
*Pulmonary function tests may not be feasible in patients <7 years of age.
ALT indicates alanine aminotransferase; AST, aspartate transaminase; DLCO, diffusing capacity of carbon monoxide; EBMT, European Society for Blood and Marrow Transplantation; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75% of forced vital capacity; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GI, gastrointestinal, P-ROM, positional, mobility, and range of motion; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

indices such as hospitalizations and care costs.[22-30] For instance, the median total all-cause costs were reported to be significantly higher for patients with steroid-refractory cGVHD, compared with matched counterparts without cGVHD, in the 1-year ($372,254 vs $219,593) and 2-year ($532,673 vs $252,909) follow-up periods.[29] A Swedish study of direct and indirect costs in patients who underwent allo-HSCT estimated cumulative total costs of €14,887,599, €20,544,056, and €47,811,835 during the first 3 years of follow-up for non-severe, mild, and moderate-to-severe cGVHD, respectively.[26] This analysis established the importance of formally grading the severity of GVHD according to established consensus severity scales,[12,31] and being vigilant during all follow-up encounters with patients post–allo-HSCT. The incremental 12-month medical cost in commercially insured pediatric patients with steroid-refractory

Table 3. Follow-Up Post-HSCT Assessments Starting from the D100 Time Point Onward

Organ System	Required Items	Threshold for Referral to Specialized Transplant Team
Skin (including nails and hair)	Conduct a complete skin, nails, and hair evaluation. The patient should be asked whether any change in appearance has been noticed	New onset of lesions suggestive of cGVHD*
Mouth	Evaluate for any lichen planus–like changes, ulcers, erythema, and restriction of mouth opening. The patient should be asked about any pain, difficulty swallowing, or dryness.	New onset of lesions suggestive of cGVHD*
Eye	Ask about any ocular symptoms (dryness, excessive tearing, foreign body sensation, redness, difficulties opening eyelids, photophobia, etc). Serial assessments by ophthalmology every 3 months during the first year post-HSCT as feasible	Symptoms suspicious of onset of ocular GVHD and change from pre-HSCT or previous post-HSCT examination
Lung	Obtain pulmonary function tests, including spirometry, lung volumes, and DLCO at D100, 1 year, and yearly. Spirometry is recommended at 6 and 9 months post-HSCT, and every 3 months in patients with cGVHD. Lung volumes and DLCO can be performed more frequently if clinically indicated	Decline in FEV_1 of ≥10% from the patient's baseline or D100 assessment; recommend short interval repeat testing (within 2-4 weeks)
Liver	Obtain bilirubin, AST, ALT, alkaline phosphatase	Rise of bilirubin or liver enzymes†
GI tract	Assess for nausea, anorexia, dysphagia, diarrhea, or weight loss	New onset of signs/symptoms suggestive of cGVHD*
Fascia/joints	Conduct functional and P-ROM assessment; for the pediatric adaption of P-ROM, see EBMT handbook/ cGVHD	In clinical trials, a 2-point difference in total P-ROM is considered clinically relevant, but as a screening measure, any change from baseline, even by 1 point, may be significant
Genitalia	Evaluate for any evidence of lichen planus–like lesions, erythema, ulcers, fibrosis, or phimosis in males (ideally women would be evaluated by a gynecologist). Ask about any change in appearance, pain, or dryness	New onset of signs/symptoms suggestive of cGVHD*

Adapted from Kitko et al, 2021.
*As per 2014 NIH consensus conference guidelines.
†Above 2014 NIH consensus conference thresholds.
ALT indicates alanine aminotransferase; AST, aspartate transaminase; D100, day 100; DLCO, diffusing capacity of carbon monoxide; cGVHD, chronic graft-versus-host disease; EBMT, European Society for Blood and Marrow Transplantation; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GI, gastrointestinal; GVHD, graft-versus-host disease; HSCT, hematopoietic stem-cell transplantation; P-ROM, positional, mobility, and range of motion; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

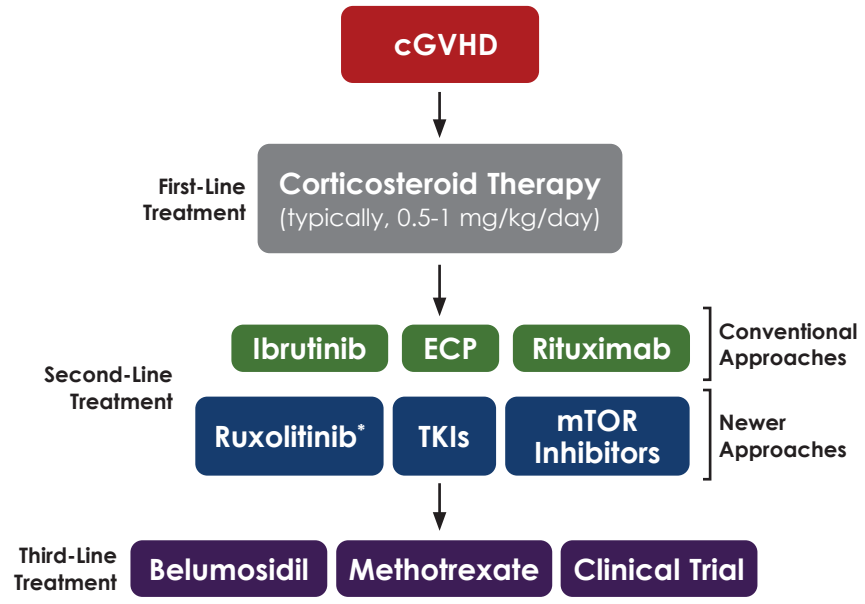
cGVHD was projected to be more than $500,000, underscoring the impact of cGVHD across age-groups.[24] Overall, the epidemiologic data highlight the continued need for novel therapies for more effective management of GVHD, especially in second and subsequent lines of therapy for this disorder following failure of first-line corticosteroid-based therapy.

GVHD pathophysiology

GVHD is thought to originate from the recognition of the recipient host as foreign by immunocompetent donor T-cells, which then results in an immune response by these donor-sensitized T-lymphocytes to allogeneic antigen-bearing host cells and subsequent destruction of host tissues.[9,25,32] Dysfunction and inadequate upregulation of regulatory T-cells, which modulate self- and foreign antigen-directed immune responses, may also contribute to GVHD.[33,34] Opportunistic viruses such as human herpesvirus-6 following allo-HSCT further increase the risk of GVHD, contributing to mortality and morbidity.[35,36]

Risk factors for aGVHD include presence and degree of HLA mismatch, sex disparity between donor and recipient, older age of the donor and/or recipient, peripheral stem-cell recipients, donor alloimmunization, absence of anti-thymocyte globulin, and seropositivity for cytomegalovirus (CMV) and Epstein-Barr virus.[8,37] Among these, HLA mismatch is the important aGVHD risk factor.[37] Similar to aGVHD, HLA mismatch, sex disparity between donor and recipient, older age, and positive CMV serology are risk factors for cGVHD.[38-41] Additional cGVHD risk factors include prior aGVHD, reduced-intensity conditioning, and high numbers of infused T-cells.[39-42] Although risk factors for the 2 forms of GVHD overlap, the risk factors and mechanisms involved in develop-

Figure 3. Proposed Algorithm Depicting Potential Therapeutic Options for cGVHD



Adapted and modified from proposed treatment algorithm in Saidu et al, 2020.[2]
*Ruxolitinib is noted as a Category 1 recommendation for treatment of steroid-refractory aGVHD and cGVHD in the NCCN guidelines.[58]
aGVHD indicates acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; ECP, extracorporeal photopheresis; mTOR, mammalian target of rapamycin; NCCN, National Comprehensive Cancer Network; TKI, tyrosine kinase inhibitor.

ment of aGVHD and cGVHD are not completely concordant.[43] For instance, total body irradiation (a high-intensity conditioning regimen) was strongly associated with aGVHD, but not cGVHD; conversely, grafting with mobilized blood cells increased the risk of cGVHD, but not aGVHD.[43] Based on these differences, along with the disparate clinical manifestations, timelines, and clinical course, aGVHD and cGVHD are considered different clinical entities in terms of their pathobiology.[44,45] aGVHD is largely considered a T-cell–mediated disorder presenting with skin, gastrointestinal tract, and liver involvement; cGVHD is biologically heterogeneous, involving multiple cell types, including B-cells, T-cells, monocytes, macrophages, and other effector cells.[44,45] Moreover, cGVHD presents with features similar to those of autoimmune diseases and can involve any organ system, with heterogeneous manifestations in various patients.[44,45]

cGVHD is thought to involve 3 phases, which often overlap, may occur interdependently or independently, sequentially or out of order, or be absent in its pathogenesis—early inflammation due to tissue injury; thymic injury and T- and B-cell dysregulation; and tissue repair and fibrosis (**Figure 2**).[46,47] In the first phase, pretransplant conditioning with cytotoxic agents, infections, and/or prior aGVHD results in the release of inflammation mediators, including cytokines and Toll-like receptor agonists. These mediators stimulate donor allo-reactive T-cell activation, resulting in acute inflammation and host tissue damage. Moreover, Toll-like receptor pathway-mediated triggering of interferon regulatory factors induces T-cell differentiation into Th1 and Th17 cells. These effector cells perpetuate tissue damage via cytolytic attack. Damage to gut tissue and the resulting release of gut microbial contents activates antigen-presenting cells. In phase 2, the persistent inflammatory stimuli amplify the interaction between antigen-presenting cells and donor-derived lymphocytes, increase the production of effector and regulatory cells, and promote their recruitment to peripheral tissues. The thymic injury and damage to secondary lymphoid organs results in increased susceptibility to cGVHD development. Thymic injury also potentiates emergence and selection of auto- and allo-reactive T-cell populations, driving the maintenance of chronic inflammation. Phase 3 is characterized by aberrant tissue repair fibrosis. The persistent inflammatory state and dysregulation of immunity from earlier processes impair regenerative pathways, resulting in excessive accumulation of components of the extracellular matrix in and around inflamed or damaged tissue. This aberrant tissue repair can promote scarring or fibrosis.

The involvement of different molecular pathways in these distinct pathogenetic phases has enabled the development of various rational agents for GVHD management, including B-/T-cell–targeted approaches, anti-inflammatory modulators, and antifibrotic agents (Figure 2).[2,46]

The clinical manifestations of cGVHD involve multiple organs/organ systems, presenting with a wide spectrum of signs and symptoms, varying in severity (clinical features of aGVHD and cGVHD are summarized in **Table 1**).[11,13]

Management of GVHD

Challenges with management GVHD and clinical course of cGVHD

Despite improved understanding of the pathogenesis of GVHD and investigation of rational approaches for prophylaxis and management of GVHD, balancing the need for preventing primary disease relapse and mitigating risk of GVHD and management of cGVHD remain challenging in practice due to the wide spectrum of clinical manifestations, which are essentially protean, the multiple organs/organ systems affected, and the lack of effective therapies, especially in

Table 4. Comparison of Recently Approved Agents for Treatment of cGVHD

	Belumosudil[75-77]	Ruxolitinib[78]	Ibrutinib[79,80]
MOA	**ROCK2 inhibitor**	**JAK inhibitor**	**BTK inhibitor**
Trial; phase	ROCKSTAR; phase 2	REACH3; phase 3	PCYC-1129; phase 1/2
Patient population	≥12 years old with persistent cGVHD manifestations after 2-5 prior systemic lines of therapy; Karnofsky or Lansky PS score ≥60; concomitant immunosuppressive medications allowed	≥12 years old; steroid-dependent or -refractory cGVHD post-HSCT	≥18 years old; steroid-refractory or -dependent cGVHD; ≤3 prior regimens (ECP/other immunosuppressants allowed)
Dose	Belumosudil 200 mg PO BID	Ruxolitinib 10 mg PO BID	Ibrutinib 420 mg PO QD
Agent(s) (no. of patients)	Belumosudil QD (n = 66) and BID (n = 66)	Ruxolitinib (n = 165) vs control (n = 164)	Ibrutinib (n = 42)
Severity (% in trial arm[s])	Mild (3% vs 0); moderate (27% vs 35%); severe (70% vs 65%)	Mild (0.6% vs 0.6%); moderate (40.6% vs 45.1%); severe (58.8% vs 54.3%)	1 organ (14%); 2 organs (57%); 3 organs (21%); 4+ organs (7%)
Efficacy			
ORR	74% and 77%*	49.7% vs 25.6%; OR, 2.99; *P* <.001 (at week 24)	69% (at median follow-up of 13.9 months)
FFS	75% (95% CI, 66-81) vs 56% (95% CI, 47-64) at 6 and 12 months, respectively	>18.6 months vs 5.7 months; HR, 0.37; *P* <.001	-
Safety	Grade ≥3 AEs 56% and 52%; included pneumonia, hypertension, and hyperglycemia	Grade ≥3 AEs 57% vs 57.6%; included thrombocytopenia, anemia, neutropenia, and pneumonia	Grade ≥3 AEs 62%; included pneumonia, fatigue, and diarrhea
FDA approval date for cGVHD indication	July 16, 2021	September 22, 2021	August 2, 2017

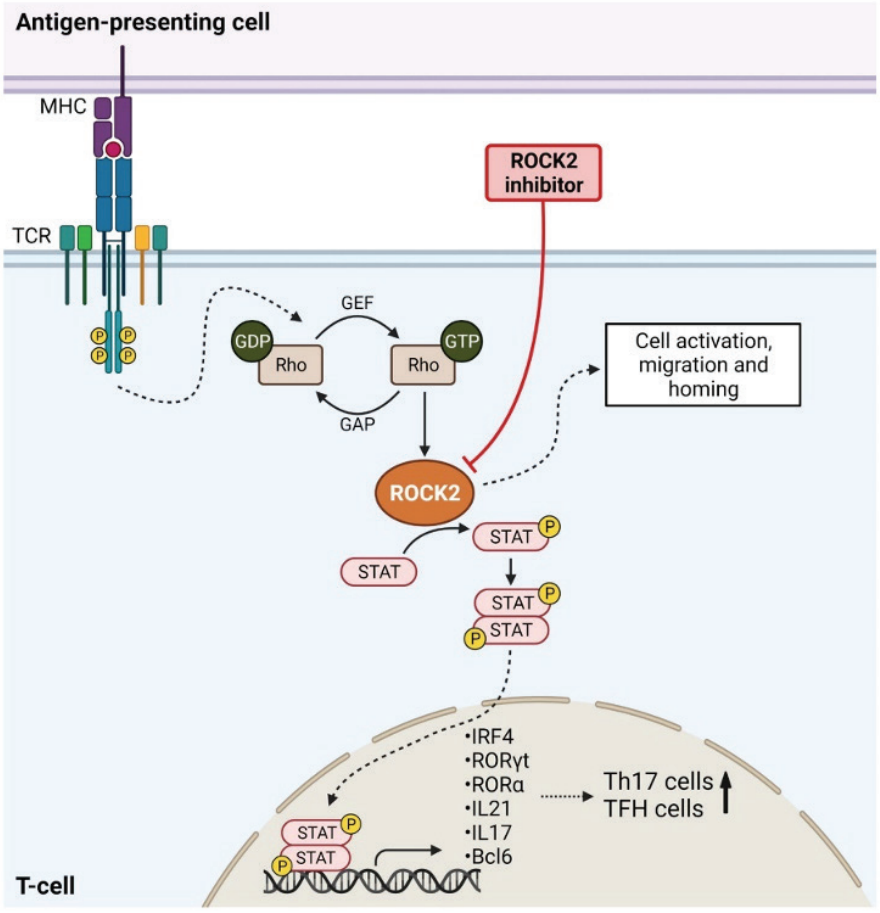
Data for the ROCKSTAR, REACH3, and PCYC-1129 summarized from primary analyses for the respective studies (Miklos et al, 2017[75]; Cutler et al, 2021[78]; Zeiser et al, 2021[79]). Please refer to the publications for further details.
*The ORRs for the subgroups with prior ruxolitinib and ibrutinib therapy were 68% (95% CI, 51-83) and 74% (95% CI, 59-86), respectively. Overall median time to response of 5 weeks (range, 4-66), indicating rapid response; 91% of responses occurred within 6 months of treatment, the remaining occurred between 6 and 12 months of treatment.
AEs indicates adverse events; BID, twice daily; BTK, Bruton tyrosine kinase; CI, confidence interval; cGVHD, chronic graft-versus-host disease; FDA, US Food and Drug Administration; FFS, failure-free survival; HR, hazard ratio; JAK, Janus kinase; MOA, mechanism of action; OR, odds ratio; ORR, overall response rate; PO, orally; PS, performance status; QD, once daily; ROCK2, Rho-associated coiled-coil–containing protein kinase 2.

second and subsequent lines of treatment. GVHD prophylaxis is traditionally involves a calcineurin inhibitor (cyclosporine A or tacrolimus) in combination with an antimetabolite (methotrexate and mycophenolate mofetil).[48] The mainstay of first-line treatment of established cGVHD remains high-dose corticosteroid therapy (typically, 0.5-1 mg/kg/day), based on their lympholytic and anti-inflammatory properties and clinical evidence.[46,49] The response rate to steroids alone is approximately 50%, with more than half of patients requiring second-line therapy within 2 years.[46] Moreover, despite GVHD prophylaxis, approximately 30% to 50% of HSCT survivors develop cGVHD.[7,11,25,46] Although no other agents have demonstrated superior efficacy to steroids in the upfront setting, alternate modalities, including extracorporeal photopheresis (ECP), other immunosuppressive agents, and psoralene-UVA, have been reported to be considered in severe cases of cGVHD, whereby they are introduced as second-line therapies in steroid-refractory GVHD.[25,46,49-52] ECP, for instance, is recommended as a second-line treatment for both aGVHD and cGVHD by the British Committee for Standards in Haematology guidelines.[25] At present, there is no consensus on the optimal second-line therapy for GVHD,[53] despite introduction of novel agents and availability of national and international guidelines (discussed in the next section).

Guidelines for GVHD management

National and international professional organizations, including the NIH, National Comprehensive Cancer Network (NCCN), American Society for Bone and Mineral Research, American Society for Blood and Marrow Transplantation (ASBMT), European Group for Blood and Marrow Transplantation (EBMT), British Oncology Pharmacy Association (BOPA), Center for International Blood and Marrow Transplant Research, British Committee for Standards in Haematology, and British Society for Bone Marrow Transplantation, have issued guidelines on the diag-

Figure 4. ROCK2 in GVHD



Adapted from Braun and Zeiser, 2021.[81]
ROCK2 mediates Th17 differentiation in GVHD. T-cell receptor stimulation results in downstream ROCK2 activation, thereby phosphorylating STAT and enabling STAT translocation into the nucleus. STAT-mediated activation of transcription of Th17-specific transcription factors thereby increases the numbers of Th17 cells. ROCK2 activation further enhances the numbers of TFH cells and increases cell migration, activation, and homing. Inhibition of ROCK2 blocks the differentiation of T-cells into TFH and Th17 cells and results in higher regulatory T-cell numbers.
GVHD indicates graft-versus-host disease; ROCK2, Rho-associated coiled-coil–containing protein kinase 2; TFH, T follicular helper.

nosis, prophylaxis, and management of GVHD and/or expounded on the critical role of the HSCT pharmacist within the multidisciplinary team involved in the care and treatment of patients with GVHD.[13,14,31,54-59] Only guidelines that have been approved by the Joint Accreditation Committee ISCT-Europe & EBMT (JACIE) or the Foundation for Accreditation of Cellular Therapy (FACT) should be used in practice. The NIH guidelines include checklists and frameworks for baseline evaluations required before transplantation and day +100 post-transplant, as well as follow-up assessments starting from day 100 post-transplant (**Tables 2 and 3**).[12-14,60] In addition, the NIH guideline updates include recommendations for educating healthcare professionals and empowering patients to actively participate in monitoring and reporting symptoms, to enable early diagnosis and treatment response monitoring.[13]

In practice, American Society of Transplant and Cellular Therapy (ASTCT) and EBMT guidelines are most commonly employed; however, with many recent therapeutic advancements in the management of cGVHD, maintenance/updating of these guidelines is often difficult. Therefore, treatment of cGVHD still relies heavily on clinician judgment and consideration of patient-specific factors.

In addition to the guidelines from the NIH, NCCN, and EBMT, additional guidance and consensus statements have also been published, including management of GVHD after cord blood transplant[57] and patient assessment templates.[16] Recently, a more tissue-specific version of the NIH response algorithm focused on GVHD in joints/fascia has also been published.[61] Although diagnostic and severity criteria for cGVHD are available, barriers and challenges to implementation of guidelines in routine practice have been reported.[51,62-65] Moreover, healthcare professionals with limited experience with cGVHD, such as primary oncologists who are not transplant specialists or other clinicians who may care for patients after HSCT completion, may be even less adept at recognizing the earliest signs and symptoms of this disorder.[13]

Treatment decision trees and algorithms

Once a GVHD diagnosis has been established and the severity has been graded, treatment depends on the organ systems involved and is predicated predominantly on first-line corticosteroid therapy. Grade 1 cGVHD is typically managed with topical steroids for local symptom control, with topical tacrolimus for steroid-resistant disease.[8] cGVHD of severity grade ≥2 requires systemic steroid therapy, most commonly with methylprednisolone; in cases involving the GI tract, nonabsorbable corticosteroids (budesonide or beclomethasone) may offer benefits over systemic steroids alone.[8] Corticosteroid therapy is tapered gradually to reduce the risk of GVHD flare.[8]

Although other agents/therapies, such as etanercept, a biologic tumor necrosis factor (TNF) inhibitor, and extracorporeal photopheresis (ECP), have been suggested as additions to corticosteroid therapy for upfront cGVHD management, to date, there is no consensus on the use of these agents in first-

Table 5. Summary of Efficacy Outcomes in ROCKSTAR Study of Belumosudil

Outcome	Efficacy Population (Belumosudil 200 mg daily; n = 65)
Overall response through cycle 7 day 1, n (%); 95% CI	49 (75%); 63%-85%
CR	4 (6%)
PR	45 (69%)
Median DOR, months; 95% CI	1.9; 1.2-2.9 months
Median time from response to death or new therapy	Not estimable
Achieved 7-point or greater decrease in the Lee Symptom Scale summary score through cycle 7 day 1, %; 95% CI	52; 40%-65%

Table adapted from Przepiorka et al, 2022.[84] Please see publication for further details.
CR, complete response; CI, confidence interval; DOR, duration of response; PR, partial response.

line therapy or on the optimal choice of treatments for second and subsequent lines of treatment.[2,53] Ibrutinib, the original Bruton tyrosine kinase (BTK) inhibitor, was the first agent approved by the US Food and Drug Administration (FDA) for second-line treatment of cGVHD and is mentioned as an approved option in NCCN and EBMT guidelines.[31,58,66] Two additional agents, ruxolitinib, the original Janus kinase (JAK) inhibitor, and belumosudil, the original Rho-associated coiled-coil–containing protein kinase 2 (ROCK2) inhibitor, have since been approved for cGVHD, after failure of 1 or 2 lines of systemic therapy and after failure of ≥2 lines of systemic therapy, respectively, in adult and pediatric patients aged ≥12 years.[67,68] Several agents are included in NCCN recommendations for use in conjunction with corticosteroids for steroid-refractory GVHD, including ruxolitinib (as Category 1 recommendation for both aGVHD and cGVHD), belumosudil (for cGVHD after failure of ≥2 prior lines of systemic therapy), and ibrutinib (for cGVHD after failure of ≥1 prior lines of systemic therapy).[58] Notably, ruxolitinib is included as a Category 1 recommended option in the second-line GVHD setting.[58] The NCCN guideline panel states that since there is no evidence to one systemic agent as preferred over another, the choice of the systemic agent should be based on institutional preferences, physician experience, agent's toxicity profile, prior treatment impact, drug interactions, convenience/accessibility, and patient tolerability.[58] In addition, several novel therapeutic agents are currently being investigated in clinical studies, including BTK inhibitors besides ibrutinib, JAK inhibitors besides ruxolitinib, proteasome inhibitors, immune cell-targeted mAbs, and antibody–drug conjugates (discussed in greater detail in the section titled **"Current and Novel Therapeutic Options for GVHD Management"**).

Table 6. Summary of Adverse Events in Belumosudil-Treated Patients in the ROCKSTAR Study

Adverse Reaction	Incidence of Adverse Reactions (n = 83)	
	All grades	Grades ≥3
Infection (pathogen not specified)	53%	16%
Asthenia	46%	4%
Nausea	42%	4%
Diarrhea	35%	5%
Dyspnea	33%	5%
Cough	30%	0%
Edema	27%	1%
Hemorrhage	23%	5%
Abdominal pain	22%	1%
Musculoskeletal pain	22%	4%
Hypertension	21%	7%
Headache	21%	0%
Viral infection	19%	4%
Pyrexia	18%	1%
Muscle spasm	17%	0%
Decreased appetite	17%	1%
Bacterial infection	16%	4%
Dysphagia	16%	0%
Arthralgia	15%	2%
Nasal congestion	12%	0%
Rash	12%	0%
Pruritus	11%	0%

Table adapted from Przepiorka et al, 2022.[84] Please see publication for further details.

Based on available data and guidelines, treatment algorithms and guidance on optimizing the treatment of cGVHD have been proposed in recent publications (**Figure 3**).[2]

Practice patterns in GVHD management

The general approach to GVHD treatment in current clinical practice relies greatly on the clinician's judgment. Treatment strategies need to account for patient-specific factors when selecting second-line (and beyond) treatment. The factors most often considered include:

- **Patient comorbidities/side-effect profile of medication** (eg, underlying atrial fibrillation/hypertension may make ibrutinib a less desirable option or a patient with poor graft function may not be an ideal candidate for ruxolitinib)
- **Patient access to care/location in relation to facility** (eg, ECP or infusion-based therapies may be more challenging for more rural patients or those living greater distances from the transplant center or another treating facility, or require

Table 7. Summary of Laboratory Adverse Events in Belumosudil-Treated Patients in the ROCKSTAR Study

Parameter	Grade 0-1 Baseline, N	Grade 2-4 Max post	Grade 3-4 Max post
Hematology			
Lymphocytes decreased	62	29%	13%
Hemoglobin decreased	79	11%	1%
Platelets decreased	82	10%	5%
Neutrophil count decreased	83	8%	4%
Chemistry			
Phosphate decreased	76	28%	7%
Gamma-glutamyl transferase increased	47	21%	11%
Calcium decreased	82	12%	1%
Alkaline phosphatase increased	80	9%	0%
Sodium decreased	83	8%	8%
Potassium increased	82	7%	1%
Alanine aminotransferase increased	83	7%	2%
Creatinine increased	83	4%	0%
Aspartate aminotransferase increased	83	1%	1%
Creatine kinase increased	83	1%	1%

Table adapted from Przepiorka et al, 2022.[84]

use of a central line that can increase infection risk and pose other problems, making oral treatments more feasible)
- **Cost** (depending on insurance, intravenous therapies may be cheaper than oral or have less burden of cost-sharing on the patient)
- **Site of organ involvement** (some organs respond better to certain agents than others; agent active based on involved organ agent may be used)

Real-world evidence and analyses of practice patterns

Real-world evidence is an important complement to the data from randomized clinical trials, especially in GVHD practice, where a significant proportion of patients in routine practice do not fit the criteria for clinical trials.[69] Limited real-world evidence is available on the practice patterns and real-world treatment outcomes with the recently introduced therapeutic options for cGVHD, including ruxolitinib and ibrutinib.[70-74] Given its recent approval and novel mechanism of action in the GVHD therapeutic space, real-world or practice-based data for belumosudil are not yet available.

"I would say we are most often using ruxolitinib as our second-line option; however, ECP as well as ibrutinib are also used. Belumosudil is usually the preferred third-line agent, but we are actually considering using it in second-line therapy in select clinical settings whereby other agents are less desirable/contraindicated. Finally, there is still an important role for clinical trials as a management alternative, and we encourage enrollment of candidate patients on those whenever possible." **– *Katie Gatwood, PharmD, BCOP***

Best practices for managing GVHD in routine pharmacy practice – GVHD treatment beyond the guidelines

"New approaches in preventing cGVHD and a better understanding of the biology and targets have led to a reduction of cGVHD incidence. The FDA has recently approved new oral treatments that are effective and less-toxic treatments. Clinical pharmacist specialists are the utmost medication experts, and their education and training in pharmacology, and drug safety can improve patient adherence and clinical outcomes by optimizing medication regimens. When HSCT patients develop cGVHD, the clinical pharmacist specialists play a critical role in recommending initial and secondary therapy. Pharmacists make their recommendations based on the several factors that may include signs and symptoms at presentation, concomitant complications, and risks for infectious complications, nephrotoxicity, relapse of malignancy, and economic impact. Given the lack of a standardized approach to managing steroid-refractory cGVHD, HSCT clinical pharmacists are essential members of the team that can help make and guide these therapeutic decisions." **– *Amir Ali, PharmD***

Current and Novel Therapeutic Options for GVHD Management

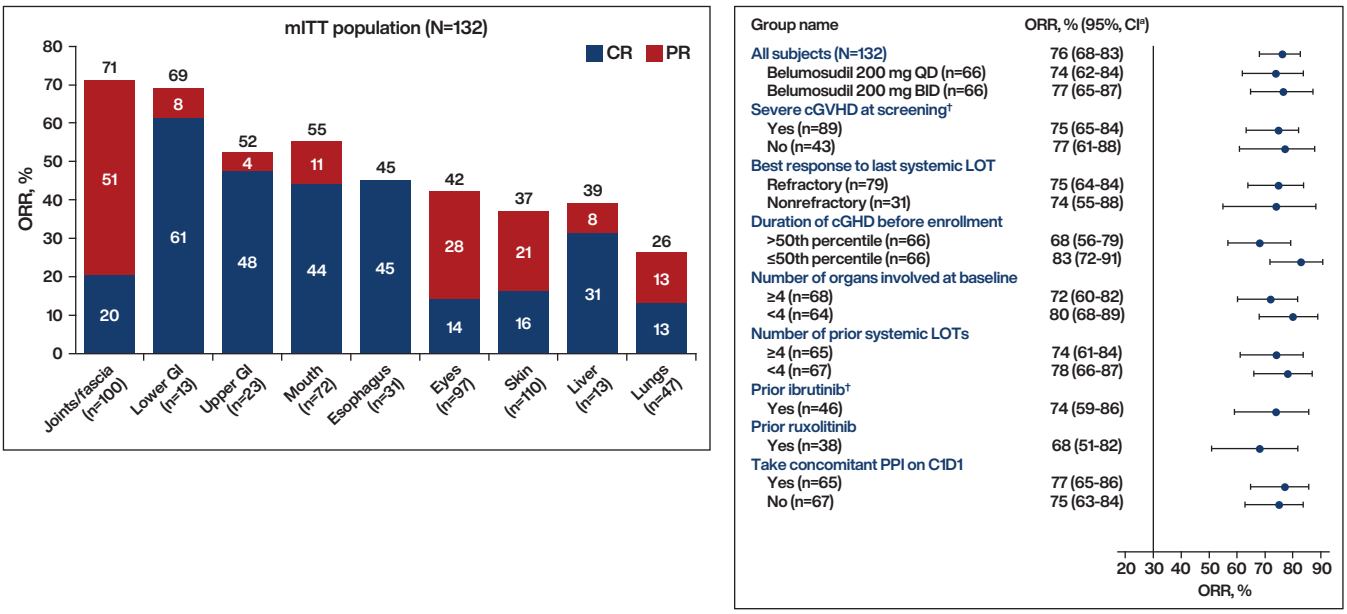
Approved agents

To date, 3 nonsteroidal agents have been approved for treatment of patients aged ≥12 years with cGVHD—the BTK inhibitor ibrutinib, the JAK inhibitor ruxolitinib, and the ROCK2 inhibitor belumosudil. Key data for these approved agents are summarized in **Table 4**.[75-80]

Belumosudil

Belumosudil is the first and only FDA-approved selective inhibitor of ROCK2, which mediates Th17 differentiation in GVHD.[68,75] Belumosudil-mediated ROCK2 inhibition blocks the differentiation of T-cells into T follicular helper (Tfh) and Th17 cells and results in higher Treg numbers; moreover, belumosudil targets the fibrosis cascade (**Figure 4**).[81-83] The clinical data from the ROCKSTAR (NCT03640481) phase 2 randomized study in patients with cGVHD who had received 2 to 5 prior lines of therapy, which

Figure 5. ORR by Organs and Subgroup Analysis in the ROCKSTAR Study



Adapted from Cutler et al, 2021.[75] Organ-specific analyses in the mITT population demonstrated ORRs in the skin, eyes, mouth, liver, lungs, joints/fascia, upper GI tract, lower GI tract, and esophagus are shown (left panel). CR was seen across all affected organs. The Forest plot of subgroup analyses of ORR in the mITT population are shown in the right panel. High ORRs were observed in all subgroups analyzed in the mITT population, and efficacy was maintained irrespective of prior treatments. The 50th percentile for duration of cGVHD before enrollment was 29 months. Response assessments performed on or after the initiation of a new systemic therapy for cGVHD were excluded from the analysis. Pooled responses across arms, unless stated otherwise.
[a]CI was calculated using the Clopper-Pearson interval (exact) method.
†Indicates stratification factors.
BID indicates twice a day; C1D1, cycle 1 day 1; CI, confidence interval; CR, complete response; cGVHD, chronic graft-versus-host disease; GI, gastrointestinal; LOT, line of therapy; mITT, modified intent-to-treat; ORR, overall response rate; PPI, proton pump inhibitor; PR, partial response; QD, once daily.

was the basis of the FDA approval, are summarized in Table 4.[75-77] In the ROCKSTAR study, belumosudil 200 mg daily and 200 mg twice daily yielded a best overall response rate of 74% (95% confidence interval [CI], 62-84) and 77% (95% CI, 65-87), respectively, with high response rates observed in all subgroups. The median duration of response was 54 weeks; 44% of subjects have remained on therapy for ≥1 years. Belumosudil 200 mg daily and 200 mg twice daily provided symptom reduction in a majority of patients (59% and 62% in subjects treated with 200 mg daily and 200 mg twice daily, respectively). Belumosudil was well-tolerated overall, with adverse events consistent with corticosteroid- and other immunosuppressant-treated subjects with cGVHD (**Tables 5-7**).[84] Notably, complete responses, per the organ-specific cGVHD response assessment as defined in the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD[85] were seen in all affected organs (**Figure 5**).[75] Moreover, 65% of subjects reduced their corticosteroid dose. Subgroup analysis indicated the belumosudil efficacy was maintained in patients with prior ibrutinib or ruxolitinib therapy (Figure 5). Overall, these data showed that belumosudil, an agent with a novel mechanism of action that is available for convenient oral dosing, with potentially few drug-to-drug interactions, was well tolerated over an extended duration and demonstrated meaningful clinical responses in patients with previously treated cGVHD.

"We are using belumosudil frequently in practice and are seeing great responses so far in patients whereby this agent is indicated. Further, this product has a manageable side-effect profile, fewer drug interactions compared to other agents, and allows for once-daily dosing (which requires reduced monitoring and potentially less frequent clinic visits, and increased patient adherence). Belumosudil is also preferred for patients with fibrotic features as this agent attenuates fibrosis. We typically reserve belumosudil for use in patients who have failed ruxolitinib or ibrutinib." ***– Katie Gatwood, PharmD, BCOP***

"As of July 2021, FDA has approved belumosudil 200 mg once daily for the treatment of cGVHD after failure of 2 or more prior lines of systemic therapies. No head-to-head studies are available at present comparing belumosudil with other cGVHD therapies. It is important to note that patients might not see an immediate response. The median time to response was 5 weeks in clinical trials, and responses were durable. It is important for pharmacists to note that belumosudil is a CYP3A4 substrate.

Table 8. Selected Studies Investigating Novel Agents in cGVHD

Agent	MOA; Target	ClinicalTrial.gov Identifier; Phase	Notes
TKIs			
Itacitinib	Selective JAK1 inhibitor	NCT03584516 (GRAVITAS-309); phase 2/3	First patient dosed in 2019; active
		NCT04200365; phase 2	Itacitinib in combination with corticosteroids; recruiting
Acalabrutinib	BTK inhibitor	NCT04198922; phase 2	Recurrent moderate–severe cGVHD
Imatinib	BCR-ABL TKI	NCT00702689; phase 2	cGVHD with sclerotic changes
mAbs			
Axatilimab	Blocks CSF-1R	NCT04710576 (AGAVE-201); pivotal phase 2	Recurrent/refractory active cGVHD, ≥2 lines of systemic therapy; 3 different doses of axatilimab to be assessed; actively recruiting
		NCT03604692; phase 1/2	Active, not recruiting as of 2/7/2022
Belimumab	Prevents binding of BAFF to the cognate receptor on B-cells	NCT03207958; phase 1	Data presented at 2022 Transplantation & Cellular Therapies Meetings; 8 of 9 patients successfully received all 7 of the preplanned doses of belimumab; after more than 20 months of follow-up (range, 20-29 months), 5 are alive with no evidence of cGVHD; 2 developed cGVHD of skin, eye, mouth, and liver
PIs			
Ixazomib	Oral PI	NCT02513498[87]; phase 2	cGVHD with progression after ≥1 systemic immunosuppressive therapies; ORR, 40% at 6 months
Carfilzomib	Irreversible PI	NCT02491359[88]; phase 2	cGVHD with progression after ≥1 systemic immunosuppressive therapies; OS was 80% at 6 months and 65% at 12 months; FFS at 12 months, 32%
mTOR inhibitors			
Sirolimus	Binds to the immunophilin FKBP4	NCT00388362; phase 2	Steroid-dependent cGVHD
Everolimus	Binds to the immunophilin FKBP12	NCT01862965 (PredEver)[89]; phase 2	In combination with prednisolone in newly diagnosed moderate or severe cGVHD; ORR, 88%

BAFF indicates B-cell activating factor; BTK, Bruton tyrosine kinase; cGVHD, chronic graft-versus-host disease; CSF-1R, colony-stimulating factor 1 receptor; FFS, failure-free survival; JAK, Janus kinase; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; OS, overall survival; PI, proteasome inhibitor; TKI, tyrosine kinase inhibitor.

Per the US prescribing information, one should increase the dose of this agent to 200 mg twice daily if given with a proton pump inhibitor or strong CYP3A4 inducers such as rifampin. Currently, there are no data available for crushing and suspending belumosudil in water for nasogastric tube administration, and, therefore, that approach is not currently recommended. However, I expect some preliminary stability data to emerge. Belumosudil is poised to become a game changer and a therapy that helps fill an unmet need for appropriate candidate cGVHD patients." ***– Amir Ali, PharmD***

Emerging Therapeutic Options

Despite recent advances, GVHD remains an area of significant unmet need for newer therapies that can improve long-term post-transplant outcomes, especially for patients who develop steroid-refractory cGVHD. Several therapeutic approaches that target the key phases of cGVHD pathogenesis, including small-molecule inhibitors of key tyrosine kinases involved in pro-inflammatory signaling and/or B-/T-cell activation, mAbs directed at immune cells, mammalian target of rapamycin (mTOR) signaling cascade inhibitors, cytokine modulators, proteasome inhibitors, and cellular therapies are currently under clinical investigation. Tyrosine kinases play a critical role in differentiation, proliferation, anti-apoptosis of various immune cells and regulation of B- and T-cell signaling pathways in GVHD.[2,81] Indeed, ibrutinib and ruxolitinib are tyrosine kinase inhibitors (TKIs) selective for the BTK and JAK1/2, respectively, that have been approved for use in GVHD indications. In addition, a new topical formulation of ruxolitinib is now being used/studied in skin cGVHD.[86]

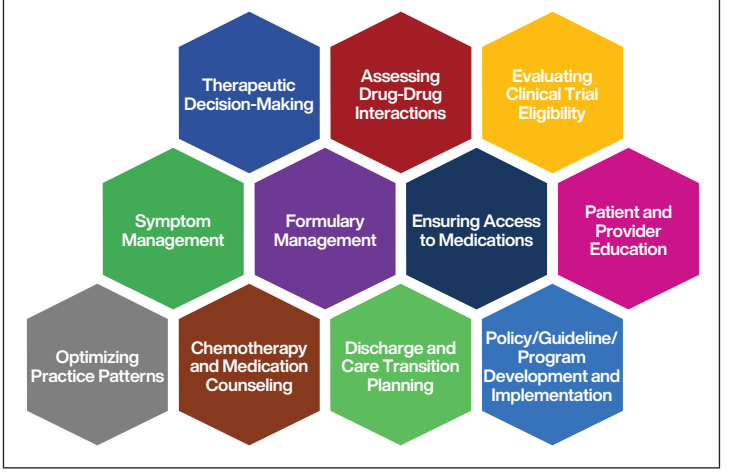
Other TKIs of interest currently being investigated in GVHD clinical studies include itacitinib, acalabrutinib, pacritinib, imatinib, nilotinib, and nintedanib.[2,81] mAbs, including those targeting immune cell surface markers and the receptor for the cytokine colony-stimulating factor 1, that are currently in GVHD clinical studies include rituximab, obinutuzumab, axatilimab, and alemtuzumab.[2] Proteasome inhibitors shown to have immune cell-modulating properties being studied in GVHD include bortezomib and ixazomib.[2] Inhibitors of the mTOR signaling pathway, such as sirolimus and everolimus, are also being investigated in GVHD, based on the strong association of this pathway in modulating T-cell activation and effector functions.[2,81] Selected key studies of emerging agents in GVHD are summarized in **Table 8**.[87-89]

Role of the HSCT Pharmacist in GVHD Management

Key role of pharmacists in the HSCT team

Given the high complexity of cGVHD, a multidisciplinary approach to patient care is necessary. Pharmacists play a key role in patient management, especially as key members of the multidisciplinary oncology care team caring for patients with hematologic malignancies undergoing HSCT.[90-93] Pharmacists are the de facto crucial clinical experts on a range of therapeutic and care aspects within the multidisciplinary HSCT team, a responsibility officially recognized by the FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration.[56] FACT-JACIE standards also require pharmacists to obtain 10 hours of HSCT-related continued education annually. The roles and responsibilities of HSCT pharmacists include: aiding in therapeutic decision-making with consideration of patient-/therapy-/disease setting–related factors; assessing drug–drug interactions and modifying therapy, as needed, such as consideration of CYP3A4 interactions with ruxolitinib, holding ibrutinib for procedures due to bleeding risk, use of proton pump inhibitors with belumosudil; medication management, including implementation of polymedication prevention measures; ensuring patient access to medications, including ensuring access to specialty pharmacy services, prior insurance authorization and copay assistance; formulary management; drug counseling for patients/caregivers to facilitate toxicity monitoring and management; evaluating patients for clinical trial enrollment including medication reconciliation, management, review for any medication-related exclusion from trials; providing education for patients/caregivers on proper medication use, adverse events, and toxicity monitoring and educating providers on novel agents; implementing symptom management and supportive care measures; driving the development and implementation of policies, guidelines, and or/internal institution-specific pharmacologic programs; optimizing practice patterns by implementing interventions that save practitioner hours (**Figure 6**).[90-94]

Figure 6. Roles and Responsibilities of the Hematopoietic Stem-Cell Transplantation Pharmacist



"As the medication experts, it is the responsibility of pharmacists to inform other members of the care team of any interventions needed to be made (ie, therapy, dose adjustments, DDIs), and continue communicating with the team and the patients in order to maintain a holistic understanding of the patient's health status and overall care." ***– Amir Ali, PharmD***

Analyses of practice interventions and patterns indicate that HSCT pharmacists and the establishment and operation of specialized clinical pharmacy programs can improve clinical and nonclinical outcomes.[95-99] For instance, implementation of a specialized clinical pharmacy program for patients who have received allogeneic HSCT was reported to be beneficial for immunosuppression drug adherence after allo-HSCT.[97] The recognition of the increasing responsibilities and the need for education of HSCT pharmacists, as well as the opportunity by experienced HSCT pharmacists themselves to disseminate their knowledge and expertise through mentoring of their peers, have been underscored by the creation and promulgation of pharmacist-specific guidelines, guideline endorsements, and formal training of pharmacists in HSCT practice.[55,100] Several national and international professional organizations have issued pharmacist-specific guidelines, endorsements, and required/recommended training for HSCT pharmacists. The American Society of Transplant and Cellular Therapy (ASTCT, formerly ASBMT) Pharmacy Special Interest Group has provided the "Fundamentals of HSCT Training Course" and the "Beyond Fundamentals" course.[100] A HSCT and Cellular Therapies Competency Passport for Pharmacists provided by the EBMT.[55] An updated training passport from BOPA designed to support pharmacists working in the adult HSCT space is available.[101]

Conclusion

GVHD is a pleiotropic multisystem complication that is common in HSCT recipients, and which remains challenging

to manage. Guidelines have been established and are periodically updated and revised for the diagnosis, monitoring, and management of GVHD. Limited treatment options are available currently for cGVHD management. Corticosteroid-based therapeutic approaches have been and remain the mainstay of first-line treatment of cGVHD. For patients who need therapy for cGVHD in the second- and subsequent-line setting, no consensus "standard-of-care" treatment exists at present. Nonetheless, the recent introduction of ibrutinib, ruxolitinib, and belumosudil have expanded therapeutic options for second and subsequent lines of treatment for cGVHD, thus markedly altering the treatment paradigm. Additional expanded follow-up in the real-world setting will help shed light on several nuances on the optimal use of these new agents and how to choose between and among them so that optimal clinical outcomes are achieved in carefully selected candidate cGVHD patients. Emerging agents predicated on other MOAs, including PIs, TKIs, and B-cell–targeted mAbs, are poised to provide additional promising avenues for improving GVHD outcomes in frontline and recurrent/steroid-refractory settings.

Pharmacists play a critical role in HSCT and GVHD management, as well as the broader education and mentoring of their peers and other clinicians in the multidisciplinary HSCT team and should be familiar with GVHD guidelines. In addition, they should seek and receive formal and informal pharmacist-specific HSCT-specific training, and, in select settings, also take the opportunity to participate in clinical and translational research in patients undergoing treatment for cGVHD in clinical studies. The multidisciplinary team approach is integral to optimizing management of GVHD and improving patient outcomes. ■

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