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A SPECIAL MEETING REVIEW EDITION

Highlights in Graft-vs-Host Disease From the 60th American Society of Hematology Annual Meeting

A Review of Selected Presentations From the 60th American Society of Hematology Annual Meeting • December 1-4, 2018 • San Diego, California

Special Reporting on:

- Results From REACH1, a Single-Arm Phase 2 Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Vs-Host Disease
- A Phase 1b Study of Intravenous Vedolizumab Plus Standard of Care for Graft-Versus-Host Disease Prophylaxis in Subjects Undergoing Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies: 6-Month Results
- Ruxolitinib Combined With Etanercept for Patients With Corticosteroid-Refractory Acute Graft Versus Host Disease After Allogeneic Stem Cell Transplantation: A Multi-Center Prospective Study
- KD025-208: A Phase 2a Study of KD025 for Patients With Chronic Graft Versus Host Disease (cGVHD)—Pharmacodynamics and Updated Results
- Effective Treatment and Low Mortality in Patients With Therapy-Refractory aGVHD After Treatment With MSC: Post-Approval Observational Data From 92 Consecutive Patients Treated With "MSC-FFM"
- Low-Dose Interleukin-2 Therapy Enhances Cytotoxicity of $CD56^{Bright}$ NK Cells in Patients With Chronic GvHD
- Serial Biomarker Monitoring Early After HCT Identifies Different Risks for Relapse and Graft-Vs-Host Disease
- Innovative Approaches to Treat GVHD Following Allogeneic Stem Cell Transplantation

PLUS Meeting Abstract Summaries

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The Steroid-dependent aGVHD Patient

Advances in graft-versus-host disease (GVHD) prophylaxis regimens have expanded the donor pool for allogeneic hematopoietic stem cell transplantation and improved patient outcomes.[1] Despite this progress, acute GVHD (aGVHD) remains one of the major challenges to successful transplant outcomes.[2]

Systemic corticosteroids (CS) have remained the standard of care for aGVHD for over 3 decades; however, less than half of patients will achieve a durable response. Long-term mortality rates for patients who do not respond to CS are estimated at 80% or higher.[3,4]

There are 2 aGVHD patient groups for which CS fail to produce an adequate response (Figure).

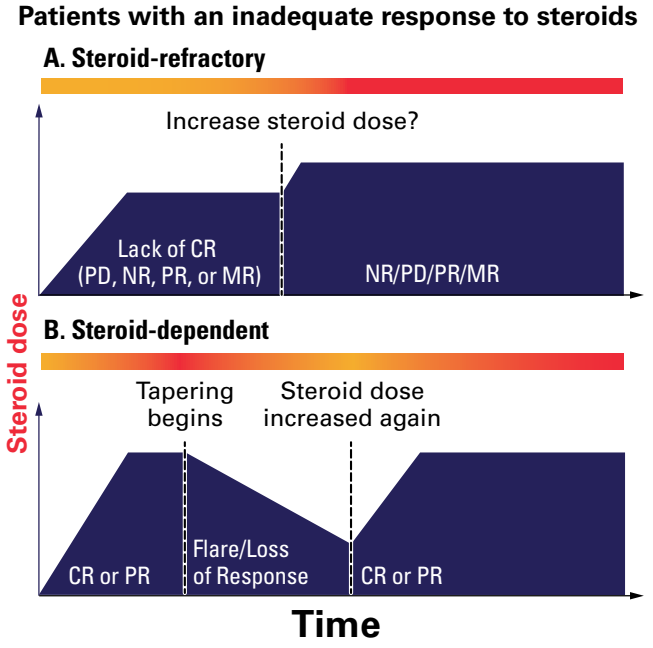

Figure. **A.** Steroid-refractory patients are those who progress or fail to improve following steroid treatment **B.** Steroid-dependent patients are those that cannot taper without flaring

Steroid-refractory or steroid-resistant (SR) aGVHD refers to worsening of aGVHD symptoms or failure to improve despite treatment with high-dose CS (Fig A).[4,5]

The American Society of Blood and Marrow Transplantation suggests that a patient be considered SR after 3 days with worsening disease manifestations of aGVHD, 1 week with ongoing grade 3 aGVHD and no improvement, or 2 weeks with ongoing grade 2 aGVHD and no improvement.[5]

Patients with steroid-dependent (SD) aGVHD are initial responders unable to taper/discontinue steroids without a return of symptoms (Fig B).[4]

Patients who are SD have not been well studied in the literature, are often excluded from clinical studies of secondary therapy for aGVHD, and have been defined inconsistently in trial inclusion criteria.[6-9]

Both SD and SR aGVHD patients face an array of potentially serious toxicities due to cumulative CS exposure.[10,11] The risk of several CS-related side effects, including infection, myopathy, and psychiatric disorders, is elevated within weeks to months of initiating treatment.[10,11] CS may also compromise the beneficial graft-versus-leukemia (GVL) effect mediated by donor lymphocytes, increasing risk of relapse.[12]

Outcomes for patients who are SD are sometimes considered more favorable than those for patients who are SR.[4,8] However, few studies have directly compared outcomes for SR and SD patients. In 2 studies that reported such data, 2-year outcomes such as overall survival and nonrelapse mortality appeared similar.[6,13]

Increasing evidence suggests that both SR and SD aGVHD patients are inadequate responders and should be managed to minimize exposure to CS and improve patient outcomes.

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Results From REACH1, a Single-Arm Phase 2 Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Vs-Host Disease

Allogeneic hematopoietic stem cell transplant (SCT) is commonly performed in patients with a hematologic disease that was not cured by standard therapy.[1] As many as half of patients who undergo allogeneic SCT will develop graft-vs-host disease (GVHD), a potentially life-threatening complication that can occur when donated hematopoietic stem cells recognize the host tissue as foreign. GVHD may present in an acute or chronic form. For acute GVHD, systemic corticosteroids are recommended as first-line treatment, but they lead to a sustained response in fewer than 50% of patients.[2,3] No therapies are approved for patients who are refractory to systemic corticosteroid therapy, and the rate of 1-year relapse-free mortality for these patients is approximately 60% to 80%.[4-6] Ruxolitinib is an oral inhibitor of Janus kinase (JAK) 1/2.[7] GVHD is characterized by high levels of proinflammatory cytokines, and activated JAK proteins are involved in activating the proinflammatory response of T cells. In mouse models, ruxolitinib reduced serum levels of proinflammatory cytokines and the severity of acute GVHD while prolonging survival and preserving the graft-vs-leukemia effect.[8-10] In retrospective studies of patients with corticosteroid-refractory acute GVHD, salvage treatment with ruxolitinib yielded promising response rates with manageable toxicity.[11,12]

Ruxolitinib was investigated in the multicenter, open-label, single-arm phase 2 REACH1 study (A Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease) of patients with GVHD refractory to corticosteroids.[13] Eligible patients were at least 12 years old and had corticosteroid-refractory acute GVHD of grade 2 to 4 based on criteria from the Mount Sinai Acute GVHD International Consortium (MAGIC).[3,14] Patients had undergone at least 1 hematopoietic SCT from any donor source for a hematologic malignancy, and showed evidence of myeloid engraftment at enrollment. The patients had received corticosteroids and at least 1 systemic treatment for acute GVHD. In addition to methylprednisolone at 2 mg/kg daily, patients received ruxolitinib at 5 mg/kg twice daily. In the absence of cytopenias, the ruxolitinib dose could be escalated to 10 mg twice daily. Corticosteroids were tapered, as appropriate. Administration continued until treatment failure, unacceptable toxicity, or death. The primary endpoint was the objective response rate (ORR) at day 28, defined as the proportion of patients with a complete response (CR), very good partial response, or partial response (PR).

As of the 6-month data cutoff, 71 patients had received at least 1 dose of ruxolitinib. At day 28, 43 patients were still receiving ruxolitinib, and 20 of these patients (46.5%) were receiving the dosage of 10 mg twice daily. At 6 months, 11 patients (15.5%) were receiving ongoing treatment. Among the 60 patients (84.5%) who discontinued treatment, the most common reasons included an adverse event (AE) in 20 patients (28.2%) and physician decision in 20 (28.2%), including 4 patients who discontinued owing to clinical improvement. Other reasons for discontinuation included death (9.9%), GVHD progression (8.5%), participant withdrawal (4.2%), and relapse (2.8%).

The 71 enrolled patients were a median age of 58 years (range, 18-73), and 50.7% were female. Graft sources

ABSTRACT SUMMARY Genetic Risk of Severe Chronic Graft-Versus-Host Disease Defined by Host-Derived CXCR3 Ligands

The role of CXCR3 and its ligands—CXCL4, CXCL9, CXCL10, and CXCL11—in severe chronic GVHD was investigated in patients who underwent allogeneic SCT and survived for at least 6 months afterward (Abstract 357). Outcomes were measured in patients who had received statin-based endothelial prophylaxis as well as in those who had not. In the training cohort, which included only patients who had not received statin-based endothelial prophylaxis, serum levels of CXCL9 at day 28 were significantly associated with the risk of severe chronic GVHD (*P*=.01). Four SNPs located in the *CXCL4* and *CXCL9* genes showed an association with the development of severe chronic GVHD. A combined SNP genetic score was calculated using these 4 loci: rs884304, rs4242209, rs3733236, and rs655328. The combined genetic score identified patients who were at high risk vs low risk of developing chronic GVHD in both the training cohort (*P*=.002) and the validation cohort (*P*=.001). Patients in the high-risk cohort also showed higher levels of CXCL9 (*P*=.004) compared with those in the low-risk cohort. Genetic variants were not impactful in patients who had received statin-based endothelial prophylaxis (*P*=.39), suggesting that this prophylaxis may reduce the risk of severe chronic GVHD by regulating serum levels of CXCL9.

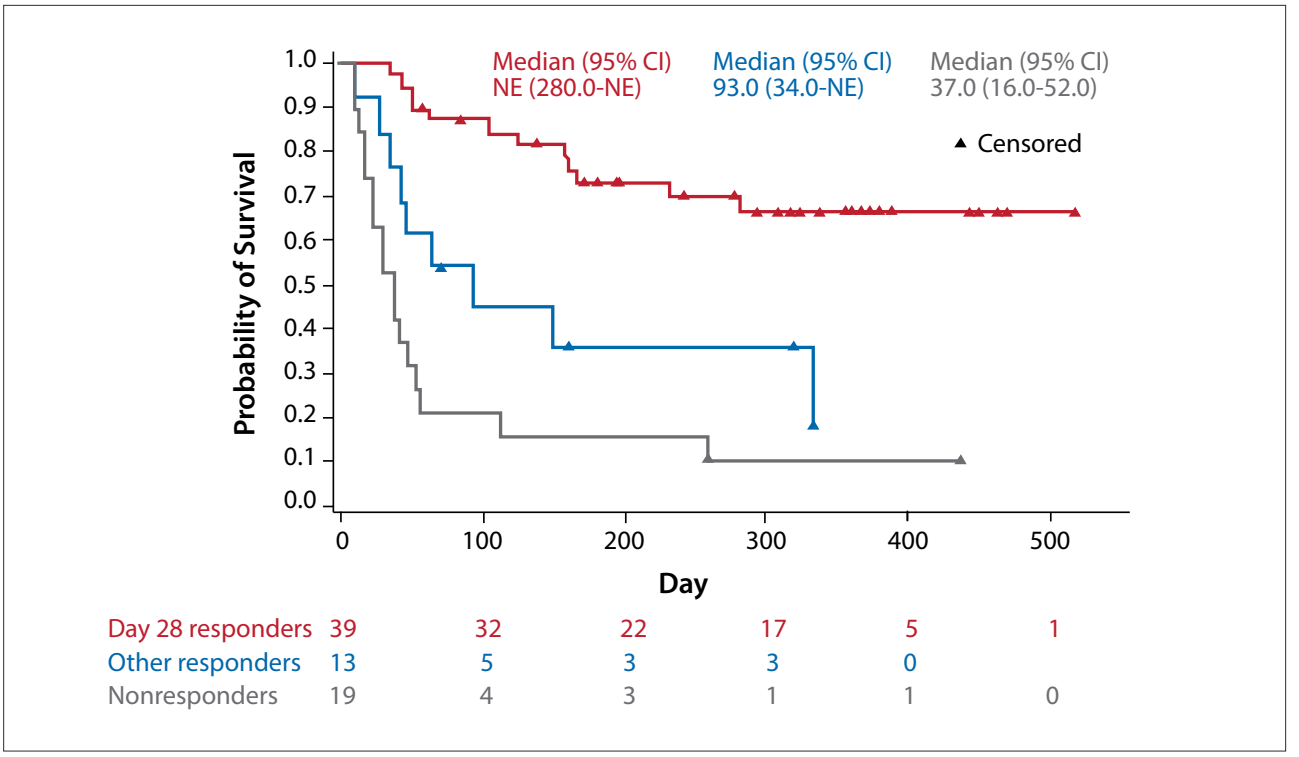

Figure 1. Median overall survival in the phase 2 REACH1 study, which evaluated ruxolitinib in combination with corticosteroids for the treatment of corticosteroid-refractory acute graft-vs-host disease. NE, not evaluable; REACH1, A Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease. Adapted from Jagasia M et al. ASH abstract 601. *Blood*. 2018;132(suppl 1).[13]

consisted of peripheral blood stem cells in 80.3%, bone marrow in 18.3%, and umbilical cord blood in 1.4%. The most common underlying malignancies included acute myeloid leukemia (28.2%), myelodysplastic syndrome (28.2%), lymphoma (12.7%), acute lymphoblastic leukemia (11.3%), and chronic lymphocytic leukemia (4.2%). The criteria for corticosteroid refractory disease included acute GVHD that had not improved after 7 days of treatment (42.3%), acute GVHD that progressed after 3 days of primary treatment (26.8%), inability to tolerate corticosteroid taper (19.7%), and, in patients who had previously received corticosteroids for skin GVHD or skin plus upper gastrointestinal acute GVHD, development of acute GVHD in another organ (11.3%). MAGIC grade III/IV disease was observed in 67.6% of patients. Cytomegalovirus (CMV) serostatus included donor (D)+/recipient (R)+ in 33.8%, D+/R– in 9.9%, D–/R+ in 22.5%, and D–/R– in 32.4%.

At day 28, the ORR was 54.9% (95% CI, 42.7%-66.8%), including a CR rate of 26.8%, a very good PR rate of 9.9%, and a PR rate of 18.3%. Among the 52 patients (73.2%) who demonstrated a response at any time during treatment, the CR rate was 56.3%. Similar response rates were observed in cohorts based on corticosteroid-refractory status. Subgroup analysis showed that patients with MAGIC grade 2 disease at enrollment had an ORR of 82.6% (95% CI, 61.2%-95.0%) compared with 41.2% (95% CI, 24.6%-59.3%) among those with grade 3 and 42.9% (95% CI, 17.7%-71.1%) among those with grade 4. Responses were observed across all organ systems and regardless of demographic variables. Among the 71 patients, the median overall survival was 232 days (95% CI, 93 days to not estimable; Figure 1). The median time to first response was 7 days. The median duration of response was 345 days for patients who exhibited a response on day 28 (lower limit, 159 days) and for other responders (lower limit, 106 days). Among patients with a response at day 28, event-free probability estimates were 81.6% at 3 months and 65.2% at 6 months. The nonrelapse mortality rate was 44.4% (95% CI, 32.5%-55.7%) at 6 months and 52.9% (95% CI, 39.6%-64.5%) at 12 months (Figure 2).

Four patients (5.6%) developed a relapse of their underlying malignancy, which was fatal in 3 cases. At day 28, 42 patients were receiving treatment with ruxolitinib plus a corticosteroid; in 24 of these patients (55.8%), the dose of corticosteroid was reduced by at least 50% from baseline. The median daily corticosteroid dose was 156.3 mg

on day 1 vs 62.5 mg on day 28.

Treatment with ruxolitinib was generally well-tolerated. The most common treatment-emergent AEs of any grade were anemia (64.8%), hypokalemia (49.3%), peripheral edema (45.1%), and decreased platelet count (45.1%). The most common grade 3/4 AEs were anemia (50.7%), decreased platelet count (39.4%), and decreased neutrophil count (32.4%). Treatment-emergent, non-CMV infections of any grade occurred in 57 patients (80.3%), with grade 3/4 infections observed in 46 patients (64.8%). Among the 14 patients with a CMV event, all had a positive CMV donor and/or recipient at baseline. No deaths were attributed to CMV events.

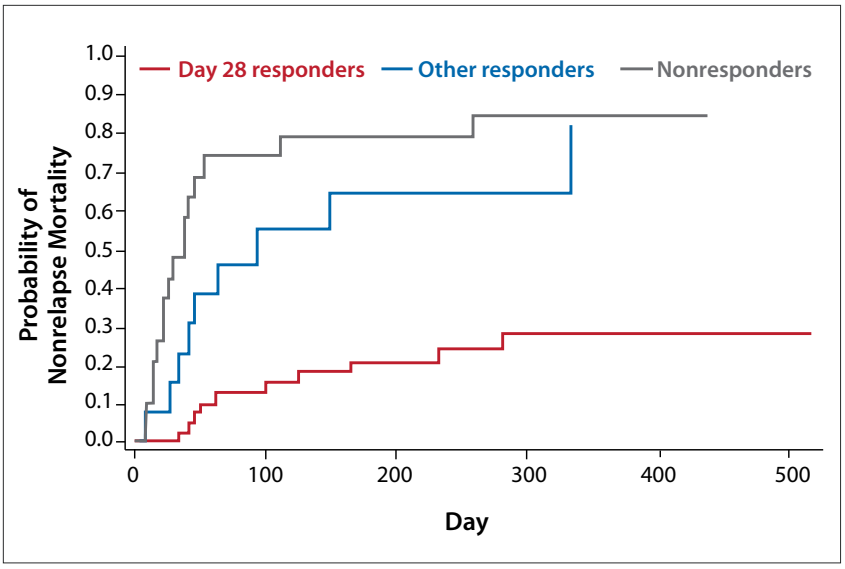

Figure 2. The rate of nonrelapse mortality in the phase 2 REACH1 study, which evaluated ruxolitinib in combination with corticosteroids for the treatment of corticosteroid-refractory acute graft-vs-host disease. REACH1, A Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease. Adapted from Jagasia M et al. ASH abstract 601. *Blood*. 2018;132(suppl 1).[13]

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A Phase 1b Study of Intravenous Vedolizumab Plus Standard of Care for Graft-Versus-Host Disease Prophylaxis in Subjects Undergoing Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies: 6-Month Results

Patients with acute GVHD of the lower gastrointestinal tract have a poor response to standard therapy as well as high morbidity and mortality. The gastrointestinal tract is a major target organ of GVHD and also serves to amplify the systemic cytokine response. The α4β7 integrin is expressed on the surface of T lymphocytes and plays a key role in allowing T cells to migrate to the gut. In a mouse model, removal of the β7 integrin subunit resulted in decreased homing of alloreactive T cells to the intestine and liver with a parallel decrease in hepatic and intestinal GVHD.[1,2] In an analysis of human blood samples taken from patients who had undergone

hematopoietic SCT, levels of α4β7 integrin were significantly increased on naive and memory T cells in those patients who subsequently developed intestinal acute GVHD.[3] Vedolizumab is a gut-selective, humanized monoclonal antibody that binds to the α4β7 integrin, interfering with the ability of T cells to home to the intestinal tissue. Vedolizumab is approved for the treatment of adults with inflammatory bowel disease.[4,5]

Prophylaxis using vedolizumab was evaluated in an open-label phase 1b study of patients undergoing allogeneic hematopoietic SCT.[6] Patients were enrolled sequentially based on their acceptability of and tolerability to treatment during days –1 to 28. Patients in cohort 1 received vedolizumab at 75 mg on days –1, 13, and 42. Patients without dose-limiting toxicities or engraftment failures could proceed to cohort 2, receiving vedolizumab at 300 mg on days –1, 13, and 42. For cohort 1, eligibility criteria included receipt of a myeloablative regimen prior to hematopoietic SCT, age between 18 and 60 years, and diagnosis of acute myeloid leukemia or acute lymphoblastic leukemia. Eligibility criteria for cohort 2 included receipt of a myeloablative regimen and age between 18 and 60 years, or receipt of a reduced intensity regimen and age between 18 and 75 years. Patients in cohort 2 could have any hematologic malignancy or myeloproliferative neoplasm. In both cohorts, donor-recipient pairs could be human leukocyte antigen–matched or –mismatched at a single locus. In cohort 1, the stem cell donors were unrelated to the patient. In cohort 2, the donors could be related or unrelated. All patients received standard GVHD prophylaxis, consisting of tacrolimus and methotrexate, in addition to vedolizumab. The study's primary objective was to describe the tolerability and safety of vedolizumab and to identify a recommended dose for administration with standard prophylactic therapy in patients undergoing allogeneic hematopoietic SCT.

ABSTRACT SUMMARY Pre-Transplant and Peri-d100 Gastrointestinal Dysbiosis Is Associated With the Subsequent Development of Chronic Graft-Versus-Host Disease

A single-center, case-control study evaluated the hypothesis that injury to the intestinal microbiota influences the development of chronic GVHD after allogeneic hematopoietic SCT (Abstract 359). The study included 55 patients with chronic GVHD, 165 case controls matched to the chronic GVHD patients by graft type, 58 patients with acute GVHD, and 71 case controls matched to the acute GVHD patients by graft source. Compared with the controls who did not develop chronic GVHD, patients who developed chronic GVHD had higher levels of *Prevotella* (*P*=.004), *Lachnospira* (*P*=.014), and *Bilophila* (*P*=.037) prior to SCT. At day 100 after SCT, patients who eventually developed chronic GVHD showed higher levels of *Akkermansia* (*P*=.03), *Streptococcus* (*P*=.05), and *Lactobacillus* (*P*=.047). Bacteria of the genera *Prevotella*, *Streptococcus*, and *Lactobacillus* were also associated with systemic sclerosis.

The trial enrolled 24 patients from 5 centers. Three patients were enrolled into cohort 1 and 21 into cohort 2. The patients' median age was 55 years (range, 18-72 years). In cohort 1, all patients had received myeloablative conditioning, and all had received a stem cell donation from an unrelated donor with matched human leukocyte antigen type. All of the stem cell donations were from the bone marrow. All patients in cohort 1 were in an initial CR. In cohort 2, 47.6% of patients had received myeloablative conditioning, 19.0% had a related donor, 95.2% had a matched donor, 71.4% had received stem cells from the peripheral blood, 81.0% were in their initial CR, and 61.9% had a comorbidity index of less than 4.

The 3 participants in cohort 1 received all 3 doses of vedolizumab at 75 mg. In cohort 2, 19 patients received all 3 doses at 300 mg, and 2 patients received 2 doses. No dose-limiting toxicities occurred. Engraftment was observed in all patients in both cohorts within 28 days. The higher dose of vedolizumab, 300 mg, was expected to achieve therapeutic concentrations for the prevention of gastrointestinal GVHD and was chosen for further clinical studies.

For patients in cohort 2, the estimated 12-month overall survival was 85% (95% CI, 59.7%-94.8%), the estimated 12-month nonrelapse mortality was 6% (95% CI, 0.6%-33.4%), and the estimated 12-month GVHD-relapse–free survival was 36% (95% CI, 14.5%-58.4%). Immunosuppression for chronic GVHD was administered to 2 of the 3 patients (67%) in cohort 1 and 8 of the 21 patients (38%) in cohort 2.

Treatment-emergent AEs of grade 3 or higher that were considered related to vedolizumab were observed in 9.5% of patients in cohort 2 and none in cohort 1. Serious treatment-emergent AEs that were considered related to treatment occurred in 1 patient (4.8%) in cohort 2. One patient in each cohort relapsed. One patient in cohort 1 and 3 patients in cohort 2 died. Infections were observed in all of the patients in cohort 1 and in 81.0% of patients in cohort 2. In cohort 2, CMV infections were observed in 7 patients (33.3%), and included 4 cases of CMV reactivation, 2 cases of CMV viremia, and 1 case of CMV colitis. At 12 months, none of the patients in cohort 1 had developed GVHD. In cohort 2, 23.8% of patients had experienced GVHD of

grade 2, 3, or 4, and 1 patient met the criteria for high-risk acute GVHD.[7] At 12 months, no patient in cohort 1 exhibited acute GVHD involving the lower gastrointestinal tract vs 3 patients (14.3%) in cohort 2.

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Ruxolitinib Combined With Etanercept for Patients With Corticosteroid-Refractory Acute Graft Versus Host Disease After Allogeneic Stem Cell Transplantation: A Multi-Center Prospective Study

The optimal salvage treatment has not been established for patients with corticosteroid-refractory GVHD after hematopoietic SCT. Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine that is produced by donor T cells. Its release after transplant plays a central role in the development of acute GVHD. Etanercept is a recombinant soluble human TNF-α receptor fusion protein. In a mouse model of hematopoietic SCT, treatment with etanercept led to improved repopulation of the bone marrow by early stem cells.[1] In a retrospective study of 15 patients with corticosteroid-refractory acute GVHD of the gastrointestinal tract, second-line treatment with etanercept yielded an ORR of 53%.[2] In a prospective study of patients with corticosteroid-refractory acute or chronic GVHD, 11 of 21 patients (52%) responded to treatment with etanercept, including 55% of patients with acute GVHD in the gastrointestinal tract.[3] Ruxolitinib is an inhibitor of JAK1/2 and has shown promise in the treatment of acute GVHD.[4]

A prospective, multicenter trial investigated the combination of ruxolitinib and etanercept in patients with corticosteroid-refractory acute GVHD after allogeneic SCT.[5] The study enrolled 31 patients with a hematologic malignancy and corticosteroid-refractory acute GVHD of grade 2, 3, or 4. Ruxolitinib was initiated at a dose of 5 mg to 10 mg, twice daily, for 2 months, followed by tapering of the dose for 1 month. Etanercept at 25 mg was administered twice per week, for 2 to 8 weeks.

At day 30 after the start of salvage treatment, the ORR was 90.3%, including a CR rate of 74.2% (Figure 3). CR rates were 93.5% in the skin, 84.2% in the liver, and 82.6% in the gut. The median time from combination therapy to best response was 12 days. Based on a multivariate analysis, the patients who received ruxolitinib within 14 days after the onset of acute GVHD had a higher CR rate than those whose treatment was delayed for more than 14 days (94.7% vs 50%; *P*=.009). Based on univariate analysis, the CR rate was 90.0% in

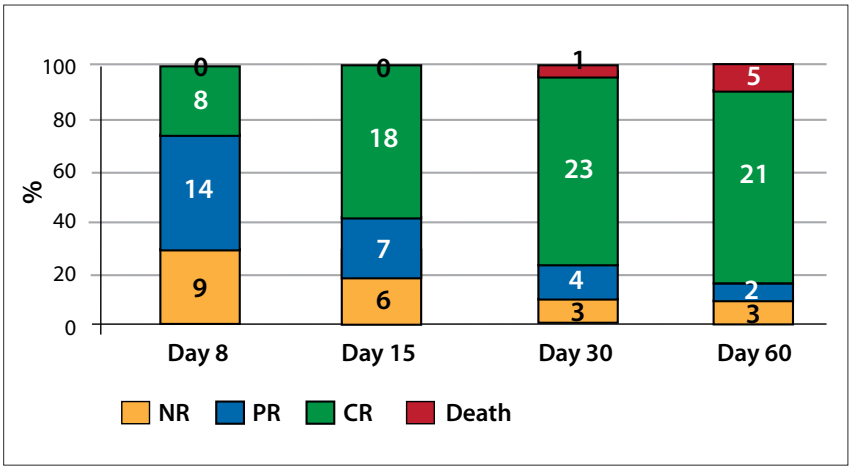

Figure 3. Responses to ruxolitinib plus etanercept among patients with corticosteroid-refractory acute graft-vs-host disease after allogeneic stem cell transplant in a prospective, multicenter trial. CR, complete response; NR, no response; PR, partial response. Adapted from Zhao Y et al. ASH abstract 4561. *Blood*. 2018;132(suppl 1).[5]

patients without gut infection vs 54.5% in those with gut infection (*P*=.037). Significant declines in the levels of interleukin (IL) 6, interferon gamma, and TNF-α were observed. The 1-year overall survival was 73.9%, and the 1-year nonrelapse mortality was 22.9%. During ruxolitinib treatment, grade 3/4 AEs included cytopenia (29.0%) and CMV reactivation (41.9%).

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KD025-208: A Phase 2a Study of KD025 for Patients With Chronic Graft Versus Host Disease (cGVHD)—Pharmacodynamics and Updated Results

Chronic GVHD is characterized by the overproduction of inflammatory cytokines and the involvement and dysfunction of both T and B cells, leading to fibrosis in the lung, liver, and skin. Rho-associated coiled-coil kinase (ROCK) mediates numerous cellular functions, including cell contraction, survival, proliferation, migration, and apoptosis.[1,2] KD025 is an orally available inhibitor of ROCK2 that reverses the pathology associated with chronic GVHD in preclinical models.[3] Treatment with KD025 was evaluated in a study of adults with corticosteroid-dependent or -refractory chronic GVHD.[4] Eligible patients had persistent, active, chronic GVHD after at least 2 months of corticosteroid treatment and were receiving glucocorticoids, with or without calcineurin. Eligible patients had received no more than 3 prior lines of treatment for their chronic GVHD. Patients were enrolled sequentially into 3 dose cohorts of KD025: 200 mg once daily (cohort 1; n=17), 200 mg twice daily (cohort 2; n=16), and 400 mg once daily (cohort 3; n=21). Key endpoints included efficacy, safety, response by organ system, and corticosteroid dose reduction.

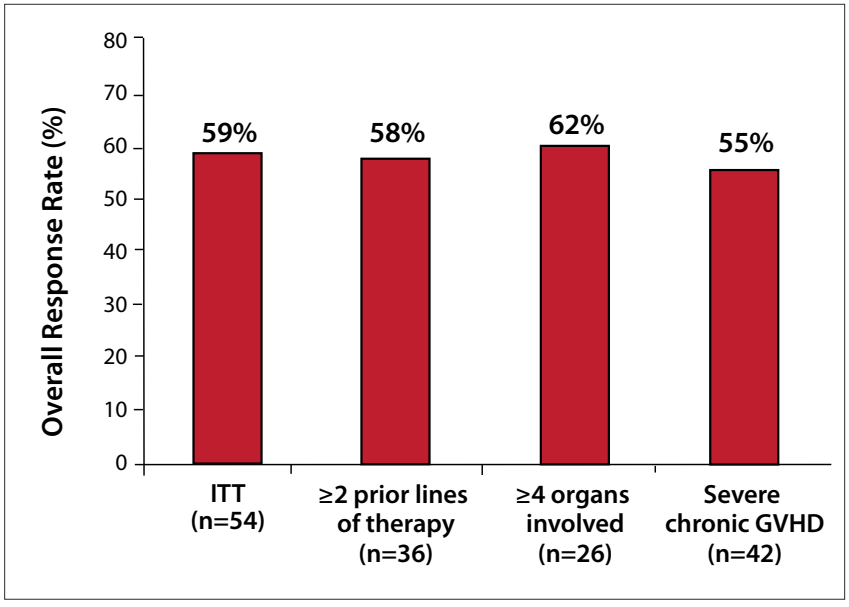

Figure 4. Responses in a phase 2a study of KD025 for patients with chronic GVHD. GVHD, graft-vs-host disease; ITT, intention-to-treat. Adapted from Jagasia M et al. ASH abstract 602. *Blood*. 2018;132(suppl 1).[4]

Across the 3 cohorts, the median age ranged from 46 to 55 years. Forty-eight percent of patients had 4 or more organs affected by chronic GVHD, and 67% of patients had received at least 2 prior lines of therapy for their chronic GVHD. The median treatment duration ranged from 27 weeks in cohort 3 to 37 weeks in cohort 1.

The ORR was 65% in cohort 1, 63% in cohort 2, and 52% in cohort 3. Three patients in cohort 3 were not available for the first response assessment. The ORR was 58% among patients with at least 2 prior lines of therapy, 62% in patients with GVHD involvement in at least 4 organs, and 55% in patients with severe chronic GVHD (Figure 4). Responses were observed across all affected organ systems. ORRs of 100% were observed

ABSTRACT SUMMARY Graft-Vs-Host Reactivity Against the Bone Marrow Is Directed Against the Hematopoietic and Non-Hematopoietic Compartments in Mice

A major histocompatibility complex–matched, minor antigen–mismatched mouse model of SCT was used to evaluate the effects of lethal irradiation and allogeneic SCT of hematopoietic stem cells, alone or in combination with T cells, on the hematopoietic and nonhematopoietic compartments of the bone marrow (Abstract 808). Compared with recipients of pure hematopoietic stem cells, mice whose grafts included hematopoietic stem cells plus T cells showed delayed recovery of hemoglobin and neutrophil levels, as well as delayed reconstitution of bone marrow B cells, bone marrow neutrophils, and total bone marrow cell counts. The presence of alloreactive T cells in the graft delayed reconstitution of the nonhematopoietic bone marrow compartment. Vascular permeability after SCT improved more rapidly in mice that received hematopoietic stem cells without T cells compared with mice whose grafts included T cells. Mice that received alloreactive T cells along with hematopoietic stem cells developed adipocytes in the bone marrow that persisted through day 56.

in the upper and lower gastrointestinal tract. ORRs ranging from 45% to 76% were observed in the skin, liver, eyes, esophagus, joints/fascia, and mouth. Two PRs were observed among 10 patients with chronic GVHD in the lung. Among patients who developed a response, 75% achieved a response by the time of the first assessment, which occurred at 8 weeks. The median duration of response was 28 weeks. Seventy-two percent of patients experienced a clinically meaningful improvement in symptoms (based on the Lee Chronic GVHD Symptom Scale).[5] Across the 3 cohorts, 7 patients completely discontinued corticosteroid treatment. The median corticosteroid dose was reduced by 44%, 23%, and 10%, in cohorts 1, 2, and 3, respectively. Tacrolimus dose reductions occurred in 67% of patients in cohort 1, 83% of patients in cohort 2, and 45% of patients in cohort 3. KD025 treatment was associated with increased levels of regulatory T cells and decreased levels of Th17 cells, consistent with the known mechanism of action of the ROCK2 inhibitor.

There were no treatment-related serious AEs or increases in the risk of infection. The AEs were generally consistent with those expected in patients with chronic GVHD treated with corticosteroids. In the intention-to-treat population of 54 patients, 94% developed an AE of any grade, and 54% experienced a grade 3/4 AE. The most common AEs of any grade were upper respiratory tract infection (26%), increased levels of alanine or aspartate transaminase (24%), fatigue (24%), and nausea (24%). Grade 3/4 AEs included increased levels of gamma-glutamyl transferase (11%), hyperglycemia (7%), anemia (6%), and dyspnea (6%). Infections of any grade included upper respiratory tract infection (26%), pneumonia (7%), influenza (6%), oral candidiasis (6%), and sinusitis (6%).

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Effective Treatment and Low Mortality in Patients With Therapy-Refractory aGVHD After Treatment With MSC: Post-Approval Observational Data From 92 Consecutive Patients Treated With "MSC-FFM"

For more than 15 years, mesenchymal stem cells (MSCs) have been investigated as a possible treatment for corticosteroid-refractory GVHD.[1,2] Despite several reports of successful outcomes with MSCs, results have been inconsistent. MSCs from different donors show considerable variation in the cells' ability to proliferate, differentiate, and suppress proliferation in the mixed lymphocyte reaction. However, because MSCs are inherently immunosuppressive, an MSC product with consistent properties presents an attractive concept for the treatment of acute GVHD. To address this need, a standardized protocol was developed to generate a

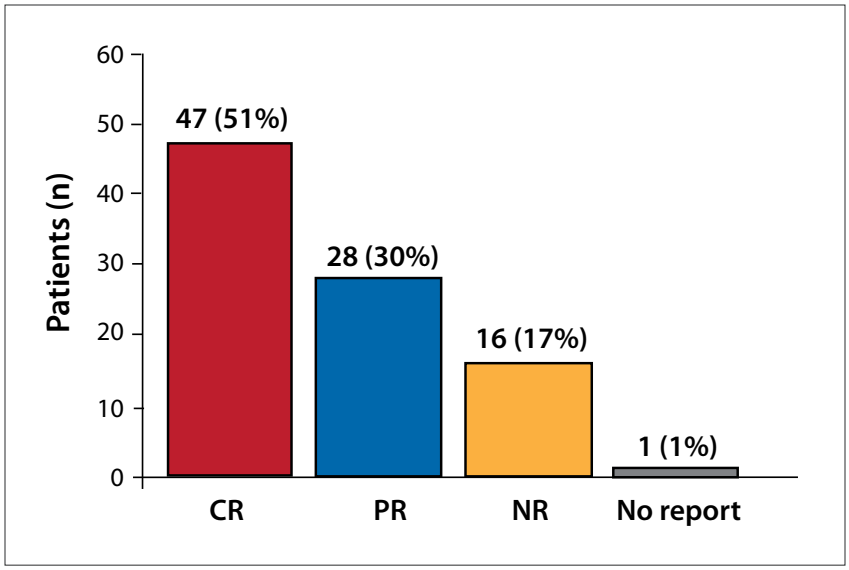

Figure 5. Response at last follow-up in a study of MSC-FFM in patients who underwent hematopoietic stem cell transplant. CR, complete response; MSC, mesenchymal stem cells; NR, no response; PR, partial response. Adapted from Bader P et al. ASH abstract 603. *Blood*. 2018;132(suppl 1).[5]

ABSTRACT SUMMARY Intestinal *Enterococcus* Is a Major Risk Factor for the Development of Acute GVHD

The role of intestinal *Enterococcus* in the development of acute GVHD was investigated in patients and mouse models of allogeneic hematopoietic SCT (Abstract 358). Weekly stool samples were collected from 1240 recipients of allogeneic hematopoietic SCT at 4 transplant centers in the United States, Germany, and Japan. Bacteria of the *Enterococcus* genus showed a relative abundance exceeding 30% in posttransplant stool samples in 20% to 60% of patients at the 4 centers. *Enterococcus* domination of the gut flora increased the risk for acute GVHD (hazard ratio [HR], 1.5; *P*=.008), reduced overall survival (HR, 1.7; *P*<.001), and was associated with a greater likelihood of GVHD-related mortality (HR, 2.2; *P*<.001). In several mouse models, a surge in the population of *Enterococcus* was observed at approximately 7 to 10 days after allogeneic SCT; however, this surge was not observed when grafts were depleted of T cells. The *Enterococcus* bloom was significantly reduced by feeding the mice a lactose-free diet.

bank of MSCs pooled from different donors, and the resulting cells (MSC-FFM) were tested in patients with refractory GVHD.[3-5]

To generate the MSC-FFM cells, mononuclear cells were isolated from the bone marrow of 8 allogeneic donors.[4] The pooled cells were expanded and tested for their MSC phenotype, trilineage differentiation, senescence, and allosuppression. The pooled MSC-FFM cells yielded superior results in the mixed lymphocyte reaction test compared with the mean calculated from results generated with MSC from each of the 8 individual donors. Different batches of MSC-FFM showed similar levels of inhibition of mononuclear cells in the mixed lymphocyte reaction test. In an initial clinical study, administration of MSC-FFM cells to 26 patients with severe, corticosteroid-resistant GVHD yielded an ORR of 77% and 2-year overall survival of 71% ±11%.[4]

The clinical efficacy and safety of MSC-FFM cells were further evaluated in a study of 92 patients from 23 centers who received hematopoietic SCT between October 2011 and October 2017.[3,5] The patients had a median follow-up of 8.6 months (range, 0.5-77.8 months). Two-thirds of the patients were ages 18 years or younger; these patients were a median age of 7.7 years (range, 0.5-18.0 years). The other 31 patients had a median age of 42.4 years (range, 18.4-65.6 years). At baseline, 88 patients (96%) had grade III/IV GVHD. Three-fourths of patients had malignant disease, and 63% had received 3 or more prior lines of therapy. The majority of stem cells were from a matched unrelated donor (61%), followed by a matched sibling donor (23%), a haploidentical donor (15%), and a mismatched unrelated donor (1%). Patients received a median of 3 MSC infusions (range, 1-5 infusions) at a mean of 1.4 MSC cells/kg (range, 0.6-4.5 MSC cells/kg). The mean cumulative dose was 4 MSC cells/kg (range, 1.0-20.7 MSC cells/kg).

At day 28 after the first MSC-FFM infusion, 26 patients (28%) had a CR, 50 (54%) had a PR, and 14 (15%) had no response. At the most recent follow-up, 47 patients (51%) had a CR, 28 (30%) had a PR, and 16 (17%) had no response (Figure 5). The estimated 48-month overall survival was 64% (95% CI, 54%-74%), the estimated 48-month nonrelapse mortality was 33% (95% CI, 23%-43%), and the estimated 48-month relapse mortality was 3% (95% CI, 0%-7%).

Analysis of patients ages 18 years or younger vs older patients showed similar outcomes based on overall survival (*P*=.182), nonrelapse mortality (*P*=.451), and relapse mortality

(*P*=.188). Outcomes among patients who had received 2 or fewer prior lines of therapy were similar to those in patients who had received 3 or more prior lines of therapy, based on overall survival (*P*=.498; Figure 6), nonrelapse mortality (*P*=.998), and relapse mortality (*P*=.145). Patients with malignant disease vs nonmalignant disease also showed similar estimated rates of overall survival (*P*=.263), nonrelapse mortality (*P*=.625), and relapse mortality (*P*=.156). MSC-FFM cells will be evaluated in a randomized trial for the treatment of corticosteroid-refractory GVHD, which will begin recruiting patients in 2019.

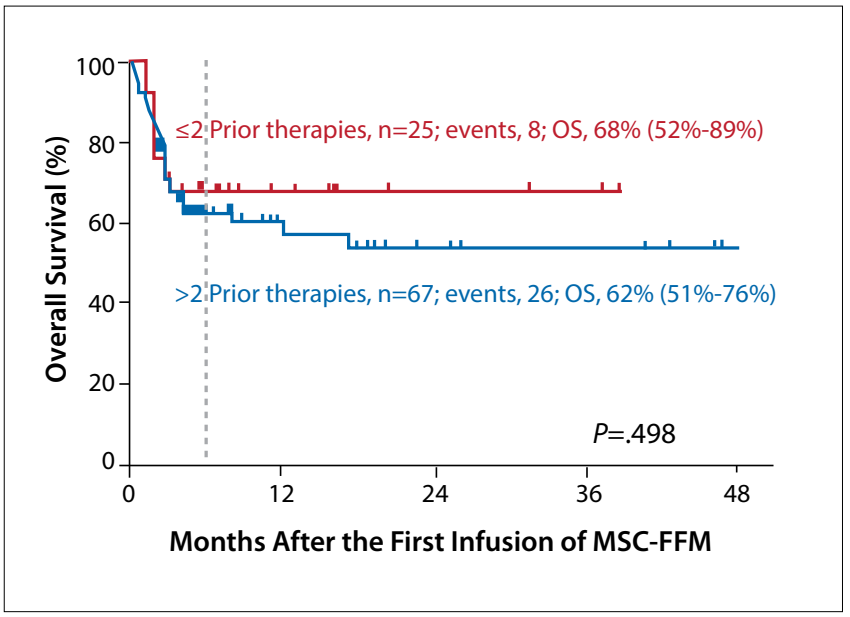

Figure 6. Overall survival according to lines of previous therapy in a study of MSC-FFM in patients who underwent hematopoietic stem cell transplant. MSC, mesenchymal stem cells; OS, overall survival. Adapted from Bader P et al. ASH abstract 603. *Blood*. 2018;132(suppl 1).[5]

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Low-Dose Interleukin-2 Therapy Enhances Cytotoxicity of CD56^{Bright} NK Cells in Patients With Chronic GvHD

Natural killer (NK) cells have the ability to kill cancer cells and are the first donor lymphocytes to recover after hematopoietic SCT.[1] NK cells that show strong expression of CD56 and little or no expression of CD16 (CD56^{bright} CD16–) perform immune regulatory functions, whereas CD56^{dim} CD16+ cells have more pronounced cytolytic activity.[2] Low doses of IL-2 induce phosphorylation of STAT5 in CD56^{bright} CD16– NK cells in vitro.[3] In patients with chronic GVHD, treatment with low-dose IL-2 preferentially expanded and activated populations of CD56^{bright} CD16– NK cells and Helios+ CD4-positive regulatory T cells. In a study of 21 patients with chronic GVHD, low-dose IL-2 combined with extracorporeal therapy yielded an ORR of 62%.[4] Extracorporeal therapy alone did not affect populations of NK cells; however, the addition of IL-2 increased levels of regulatory T cells and NK cells.

The function of CD56^{bright} CD16– NK cells expanded by low-dose IL-2 was further characterized in a clinical trial of 10 patients with chronic GVHD who also received extracorporeal therapy.[5] The patients' median age was 62 years (range, 34-76 years), and 6 were female. Global chronic GVHD severity was moderate in 9 patients and severe in 1. The median time from hematopoietic SCT was 697 days (range, 340-2842 days), and the median time from onset of chronic GVHD was 215 days (range, 58-1325 days). At week 8, responses included 2 PRs and 8 cases of stable disease.

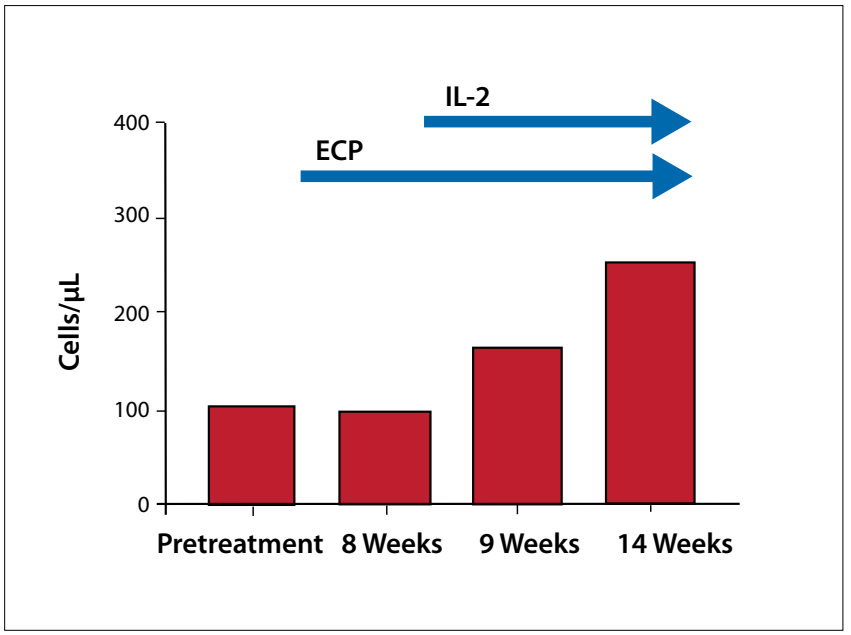

Figure 7. Proportional change in NK cells during treatment with ECP plus low-dose IL-2 therapy among patients treated with chronic graft-vs-host disease. ECP, extracorporeal therapy; IL, interleukin; NK, natural killer. Adapted from Kubo T et al. ASH abstract 606. *Blood*. 2018;132(suppl 1).[5]

ABSTRACT SUMMARY Sequential Infusion of TCRαβ- and CD45RA-Depleted Haploidentical Progenitor Cells Is Safe and Allows for Rapid Immune Reconstitution in Pediatric Patients With Recurrent Hematological Malignancies

Depletion of T cells that express T-cell receptor αβ or CD45RA prior to allogeneic SCT can reduce the incidence of GVHD. A phase 2 clinical study investigated the safety and efficacy of infusing 2 haploidentical allogeneic grafts—1 depleted of T-cell receptor αβ T cells and the other depleted of CD45RA T cells—in pediatric patients with hematologic malignancies of very high risk and whose disease recurred after a prior allogeneic hematopoietic SCT (Abstract 4575). After receipt of the 2 grafts, all patients experienced rapid engraftment of the donor cells. The level of regulatory T cells was significantly higher among patients who received prophylaxis with sirolimus vs tacrolimus ($P<.05$). Grade 3/4 GVHD was observed in 2 of 13 patients who received sirolimus prophylaxis vs 4 of 5 patients who received tacrolimus prophylaxis. After a median follow-up of 11.5 months, 78% of patients were alive.

At week 16, responses included 7 PRs and 3 patients with stable disease. Patients received extracorporeal therapy twice weekly during weeks 1 to 8. Extracorporeal therapy was continued with the addition of daily low-dose IL-2 (1×10^6 IU/m^2) during weeks 9 to 16. For lymphocyte evaluation, single-cell mass cytometry was used with a panel of 26 cell surface markers to identify specific lymphocyte populations and 9 intracellular markers to evaluate functional status and activation of signaling pathways.

No changes to NK cell markers or levels of NK cells were observed during the initial 8 weeks of extracorporeal therapy. After 1 week of treatment with low-dose IL-2, the NK cell population began to rise, with continuing increases observed through week 14 (Figure 7). Throughout the same time period, levels of CD56^{bright} NK cells increased, whereas levels of CD56^{dim} NK cells decreased. Compared with baseline values, expression of Ki-67 in CD56^{bright} NK cells increased and peaked during the first week of low-dose IL-2 treatment, followed by a return to baseline by week 14. A similar pattern was observed for the expression of NK cell activating receptors, including ILT-1, NKp30, and NKp46. The level of the inhibitory cell receptor NKG2A also increased in CD56^{bright} NK cells after administration of low-dose IL-2. These changes were not observed in CD56^{dim} NK cells, and CD56^{dim} cells were generally less affected by treatment with IL-2. Based on functional assays, the cytolytic activity of CD56^{bright} cells increased after low-dose IL-2 treatment compared with baseline and exceeded that of CD56^{dim} cells.

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Serial Biomarker Monitoring Early After HCT Identifies Different Risks for Relapse and Graft-Vs-Host Disease

A biomarker algorithm based on levels of ST2 and REG3α in blood samples taken on day 7 after hematopoietic SCT can identify patients who are at high risk vs low risk for lethal GVHD or nonrelapse mortality.[1] Patients identified as high risk were more likely to develop GVHD-related mortality (18% vs 4%; *P*<.001) and severe gastrointestinal GVHD (17% vs 8%; *P*<.001). A follow-up study evaluated whether sequential monitoring at 3 time points during the first 28 days after hematopoietic SCT could improve the accuracy of predicting which patients were most likely to experience GVHD.[2] The study included clinical data and research samples from 19 bone marrow transplant centers. The study included 702 patients in the training set and 906 in the validation set. Patients in the training set underwent hematopoietic SCT from January 1, 2006 through June 30, 2015, and patients in the validation set underwent hematopoietic SCT from July 1, 2015 through May 1, 2017. Patient serum samples were analyzed for levels of ST2 and REG3α up to 3 times, on days 7, 14, and 28, and/or at the onset of GVHD within the first 28 days after transplant. Patients who were categorized as high risk for the development of lethal GVHD at any time remained in that category for the duration of the study and were not retested.

Receiver-operator characteristic curves showed an improved ability to predict both nonrelapse mortality and lethal GVHD with 3 days of sequential testing vs a single test on day 7 after hematopoietic SCT. Patients in the training set had a higher rate of nonrelapse mortality (16% vs 13%; *P*=.08), a lower proportion of haploidentical donors (1.4% vs 11.1%; *P*<.001), and a higher rate of myeloablative conditioning therapy (74.1% vs 61.8%; *P*<.001). In the validation set, 28% of patients were identified as high risk and 72% as low risk. Patients categorized as high risk were more likely to develop stage 3/4 gastrointestinal GVHD (*P*<.001; Figure 8) or grade 3/4 GVHD (*P*<.001). The high-risk and low-risk cohorts had similar rates of relapse (*P*=.93), but the high-risk cohort had a higher rate of lethal GVHD (*P*<.001; Figure 9) and a lower rate of relapse-free survival (*P*<.001).

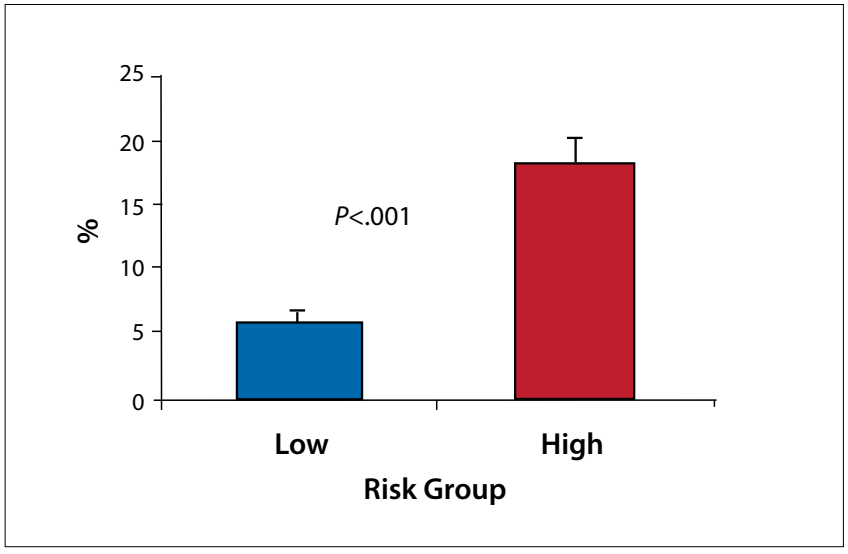
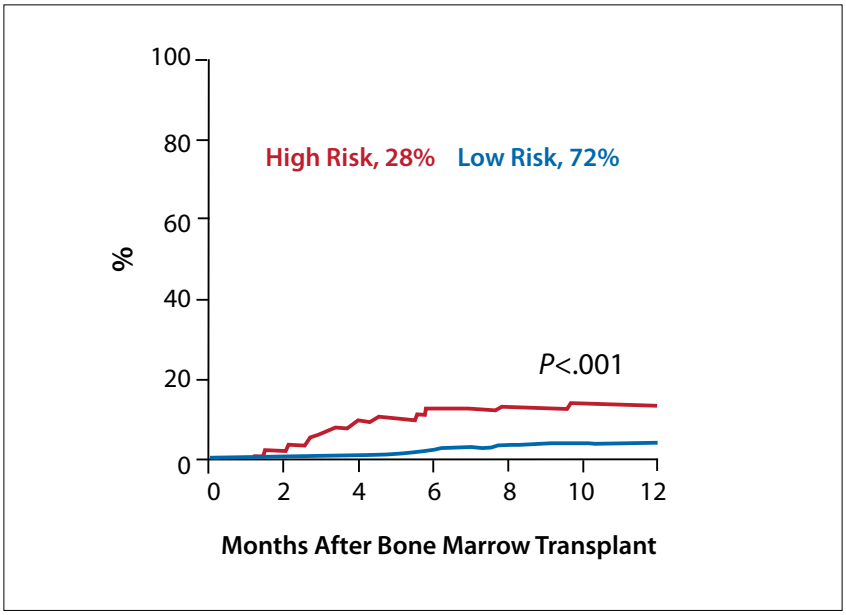


Figure 8. In a study of serial biomarker monitoring early after hematopoietic stem cell transplant, patients categorized as high risk were more likely to develop stage 3/4 gastrointestinal graft-vs-host disease. Adapted from Aziz MD et al. ASH abstract 356. *Blood.* 2018;132(suppl 1).[2]

Most of the patients who undergo allogeneic hematopoietic SCT do not develop GVHD during the first 28 days after transplant. In these patients, particularly those identified as low risk, relapse is much more likely than GVHD to cause transplant failure. In the validation cohort, 53% of patients did not develop GVHD by day 28 and were low risk at all 3 evaluations of GVHD biomarkers. To identify patients who were more likely to experience relapse vs nonrelapse mortality, GVHD biomarkers were measured at day 28 in patients without GVHD. In the validation set of 655 patients who did not develop GVHD within 28 days after transplant, 11% of patients were at high risk for relapse and 89% were at low risk. The high-risk cohort had a significantly higher rate of nonrelapse mortality (*P*<.001) and a lower rate of relapse-free survival (*P*<.001).

A disease risk index was previously developed to predict overall survival in patients who have undergone allogeneic hematopoietic SCT.[3] The disease risk index was used to categorize patients with no GVHD by day 28 and who were low risk according to GVHD biomarker analysis. Thirty-two percent of patients had a high disease risk index score, 63% had an intermediate score, and 5% had a low score. The risk for relapse was higher than the risk for nonrelapse mortality,

Figure 9. Rates of lethal graft-vs-host disease in a study of serial biomarker monitoring early after hematopoietic stem cell transplant that categorized patients as high risk or low risk. Adapted from Aziz MD et al. ASH abstract 356. *Blood*. 2018;132(suppl 1).[2]



particularly in the groups of patients with a high or intermediate score.

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Innovative Approaches to Treat GVHD Following Allogeneic Stem Cell Transplantation

Among patients who die after undergoing allogeneic hematopoietic SCT, the cause is GVHD in approximately 7% (Figure 10). In an Education Program at the 60th American Society of Hematology annual meeting, Dr Robert Zeiser discussed novel approaches to the treatment of acute and chronic GVHD that develops after allogeneic hematopoietic SCT.[1-3] Early studies of ruxolitinib in the acute GVHD setting were predicated on the idea that inhibition of the JAK1/2 proteins could interfere with activation of effector T cells and reduce proinflammatory cytokines that are associated with manifestations of GVHD, such as inflammation, tissue damage, and fibrosis.[4] In an allogeneic hematopoietic SCT mouse model with a major mismatch of the major histocompatibility complex, treatment with ruxolitinib was associated with superior weight maintenance and significantly improved survival compared with controls (P<.0001). At days 8, 14, and 29 after allogeneic hematopoietic SCT, GVHD histology scores were significantly better in the small intestine, large intestine, and liver with ruxolitinib vs the controls (P<.05). Ruxolitinib significantly decreased inflammatory cytokine production after allogeneic hematopoietic SCT while increasing the production of regulatory T cells. Other studies confirmed the concept that JAK1/2 blockade could reduce GVHD while preserving graft-vs-tumor effects, and retrospective studies showed responses in patients with corticosteroid-refractory GVHD.[5-8] The mechanism by which JAK inhibition reduces GVHD depends on inhibition of the C2TA/major histocompatibility complex class II axis in dendritic cells.[9] JAK1/2 inhibition also affects neutrophil migration, an early event in the development of acute GVHD.[10] Conditioning therapies administered prior to SCT can damage the intestinal tract, which in turn promotes inflammation and contributes to the onset of acute GVHD. During the onset of acute GVHD, neutrophils migrate to the ileum and then to mesenteric lymph nodes, where they affect T-cell expansion through antigen presentation by major histocompatibility complex class II molecules. Inhibition of JAK1/2 decreased the migration of neutrophils into the mesenteric lymph nodes and reduced major histocompatibility complex class II expression. JAK1/2 inhibition is being investigated in prospective, randomized phase 3 trials in patients with corticosteroid-refractory GVHD.[11-13]

Inhibition of mitogen-activated protein kinase (MEK) and Bruton tyrosine kinase has shown promise in the management of GVHD. MEK acts downstream of RAS, and thus plays a role in mediating the survival, activation, and migration of lymphatic cells. The RAS/MEK/ERK pathway is preferentially activated in naive and central memory human T cells. In vitro inhibition of MEK preferentially reduced cytokine production and alloreactivity of naive and central memory human T cells without affecting virus-directed T cells.[14] In a murine major histocompatibility complex mismatch model

in which all mice develop GVHD after hematopoietic SCT, treatment with selumetinib significantly reduced GVHD-associated mortality and significantly increased median overall survival vs the control treatment (34 vs 10 days; *P*=.01). Ibrutinib inhibits the kinase activity of Bruton tyrosine kinase and is approved by the US Food and Drug Administration for the treatment of adults with chronic GVHD after 1 or more lines of systemic therapy.[15] The approval was based on results of a multicenter, open-label study in patients with active, corticosteroid-refractory, chronic GVHD.[16] Forty-two patients treated with as many as 3 prior therapies received daily ibrutinib monotherapy. After a median follow-up of 13.9 months, two-thirds of patients exhibited a response, and 71% of responding patients sustained a response for at least 20 weeks. Responses were observed across all affected organs. The median use of corticosteroids decreased in responders from 0.29 mg/kg daily at baseline to 0.12 mg/kg daily at week 49. Five patients completely discontinued corticosteroid therapy. Ibrutinib reduced fibrosis, symptoms of chronic GVHD, and markers of inflammation in the plasma. The most common AEs of any grade were fatigue, diarrhea, muscle spasms, nausea, and bruising.

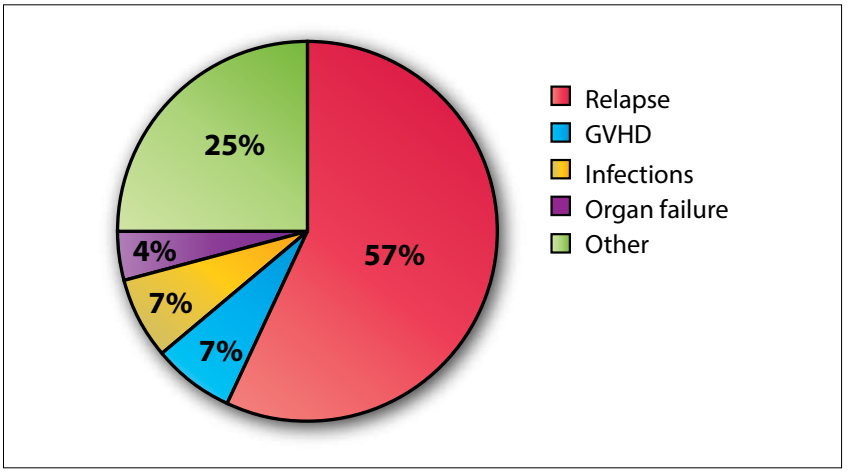

Figure 10. Causes of death after allogeneic hematopoietic stem cell transplant. GVHD, graft-vs-host disease. Adapted from Zeiser R. Innovative approaches to treat GVHD following allogeneic stem cell transplantation. Paper presented at: the 60th Annual Meeting of the American Society of Hematology; San Diego, California; December 1-4, 2018.[1]

ABSTRACT SUMMARY High Pre-HCT Exposure to Thymoglobulin Is Associated With a Low Incidence of Relapse

Levels of rabbit anti–T cell globulin (ATG) levels and their relationship with disease relapse and GVHD were evaluated in 153 leukemia patients who underwent their first allogeneic hematopoietic SCT (Abstract 4605). GVHD prophylaxis included rabbit ATG (0.5 mg/kg, day –2; 2 mg/kg, day –1; and 2 mg/kg, day 0) administered prior to graft infusion. Patients with an ATG area under the curve that was above the median before the SCT had a lower incidence of relapse (subdistribution HR, 0.430; *P*=.029) and an improved relapse-free survival (HR, 0.534; *P*=.040) vs those with a lower ATG level. However, in samples taken after transplant, a larger ATG area under the curve was associated with a higher incidence of relapse (subdistribution HR, 1.470; *P*=.302). A greater ATG exposure after SCT was significantly associated with a lower incidence of GVHD (subdistribution HR, 0.462; *P*=.005).

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Highlights in Graft-vs-Host Disease From the 60th American Society of Hematology Annual Meeting: Commentary

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Presentations in graft-vs-host disease (GVHD) at the 60th American Society of Hematology (ASH) annual meeting may impact clinical care. Data were presented on the use of ruxolitinib and vedolizumab, as well as novel treatment strategies.

I presented results from the REACH1 trial (A Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease), a single-arm phase 2 study of ruxolitinib in combination with corticosteroids for the treatment of patients with corticosteroid-refractory acute GVHD.[1] Approximately 60% of patients who undergo an allogeneic transplant develop acute GVHD. In approximately half of these patients, the disease is refractory to corticosteroids. Four subsets of patients with corticosteroid-refractory acute GVHD were considered eligible for the study: (1) Those with worsening acute GVHD after 3 days of 2 mg/kg methylprednisolone equivalent. (2) Those with no improvement after 7 days of 2 mg/kg methylprednisolone equivalent. (3) Those who developed new acute GVHD organ involvement during treatment with 1 mg/kg or higher methylprednisolone equivalent for acute GVHD of the skin alone or the skin plus upper gastrointestinal (GI) tract. (4) Those unable to tolerate a corticosteroid taper.

The study showed that when ruxolitinib was effective, the time to response was fairly quick, at a median of 7 days. Overall response was defined as a complete response, a very good partial response, or a partial response at day 28 after enrollment in the study. The rate of overall response was 54.9%. Another key endpoint was the duration of response. Among the patients who responded to ruxolitinib, the duration of response was fairly robust, at a median of 345 days. The median survival of the patients who responded was close to a year.

There were no overt signals regarding any treatment-emergent adverse events with ruxolitinib, including the potential for infection. There was a high rate of treatment-emergent infections (80%), but this finding is consistent with patients who have corticosteroid-refractory acute GVHD. There was no toxicity signal that could be attributed specifically to ruxolitinib. Therefore, it appeared that ruxolitinib was safe and effective when used in combination with corticosteroids for the treatment of patients with corticosteroid-refractory acute GVHD.

Dr Yanmin Zhao presented results from a multicenter, prospective study evaluating ruxolitinib combined with etanercept in patients with corticosteroid-refractory acute GVHD after allogeneic stem cell transplant.[2] This study was performed in China, where etanercept is used for corticosteroid-refractory acute GVHD.[3] In the United States, however, etanercept is not widely used because it increases the risk of infection.[4] At Dr Zhao's institution, they combined the interleukin-25 blocker basiliximab with etanercept for corticosteroid-refractory acute GVHD, and they used data for 31 patients treated with this strategy as a historical cohort. The idea of using ruxolitinib combined with etanercept was to block 2 critical signaling pathways for the activated T cells: the Janus kinase 1/2 pathway and the tumor necrosis factor–α pathway. This treatment led to an impressive rate of complete response/partial response of 90.3%, with 74.2% of patients achieving a complete response. That is an outlier response. Among patients in the historical cohort treated with basiliximab and etanercept, the overall response rate was also 90.3%. The researchers noted that the response rate with ruxolitinib plus etanercept was not statistically higher than that in the historical cohort, but that this combination led to a quicker response, at a median of 11 days, vs 17 days with basiliximab and etanercept. This difference was statistically significant.

Among patients treated with ruxolitinib plus etanercept, 9 developed severe infection (defined as grade 2 or higher), such as tuberculosis, cytomegalovirus pneumonia, invasive fungal

infection, and human herpesvirus–6 acute limbic encephalitis. These infections suggest the presence of severe immunosuppression, raising the question of whether this treatment is too immunosuppressive and might lead to opportunistic infections.

Another concern is that this center has high rates of complete response in the historic data. The question, however, is whether the initial complete response translates into a longer-term benefit. They report that the ruxolitinib/etanercept combination led to a 1-year overall survival rate of 73.9%, with a 1-year nonrelapse mortality rate of 22.9%. This rate of overall survival is unusually high for these patients. More mature data are needed for confirmation. If this approach can be validated in another study, it may be interesting.

I was the lead investigator of KD025-208, a phase 2a study of KD025 for patients with chronic GVHD.[5] KD025 inhibits ROCK2, an isoform of Rho-associated coiled-coil kinase (ROCK), and a signaling molecule at the fulcrum of T-cell alloreactivity and the counter-regulatory mechanisms. Preclinical science suggested that the inhibition of ROCK2 could sway T cells toward an anti-inflammatory T-regulatory phenotype, which could restore homeostatic balance in a patient with chronic GVHD.[6] Preclinical modeling data suggested that this strategy could work in patients with chronic GVHD.[7]

These preclinical data provided the rationale for a phase 2a study.[5] The study enrolled 54 patients into 3 cohorts: 200 mg once daily, 200 mg twice daily, and 400 mg once daily. The response rates were approximately 60%. No incremental dose effect was seen in the 400 mg once-daily arm. Responses were seen across all organ systems, and there were no reports of chronic GVHD. GVHD is a pathologic disease that impacts multiple organs, including the eyes, mouth, skin, lungs, joints, fascia, genitourinary tract, liver, esophagus, stomach, and small intestine. There were no overt safety signals in the study. A follow-up study, KD025-213, is now under way.[8] This randomized 2-arm study will evaluate KD025 at 200 mg once daily and 200 mg twice daily.

Dr Yi-Bin Chen presented the 6-month results of a phase 1b study of intravenous vedolizumab plus standard of care for prophylaxis of GVHD in patients undergoing allogeneic hematopoietic stem cell transplant for hematologic malignancies.[9] Soon after an allogeneic transplant, the donor T cells that become alloreactive in the first several days posttransplant start to develop homing markers. This process decides the fate of those alloreactive T cells, determining whether they go to the skin or to the GI tract. Pathologically, GI GVHD is the more severe entity, potentially leading to nausea, vomiting, diarrhea, hypoalbuminemia, malnutrition, and infection. There is an unmet need for a targeted therapy to manage GI GVHD. Once GI GVHD develops, it is difficult to treat. Vedolizumab is a monoclonal antibody that targets an integrin molecule on these leukocytes, preventing them from reaching the GI tract. The study from Dr Chen and colleagues evaluated 2 dose levels: 75 mg and 300 mg. The use of vedolizumab in other indications, such as inflammatory bowel disease, suggests that the 300-mg dose is more effective.[10] However, given that this study was phase 1 and evaluating a new indication, a lower-dose was also evaluated in cohort 1. The study enrolled 3 patients with a variety of diagnoses into the low-dose cohort. The overall survival rate was 67%. The incidence of nonrelapse mortality was zero. The rate of grade 2 to 4 acute GVHD-free survival was 67%, and the rate of grade 3 to 4 acute GVHD-free survival was 67%.

The study enrolled 21 patients into the 300-mg cohort. The overall survival was 85%, with a nonrelapse mortality rate of 6%. Grade 2 to 4 acute GVHD-free survival was 63%, and grade 3 to 4 acute GVHD-free survival was 80%. In this cohort, only 19% of the patients developed grade 2 to 4 acute GVHD at 6 months after transplant. One case was grade 2, 1 patient developed skin-only involvement, and 2 patients had skin and lower-GI involvement. Another patient with grade 3 GVHD had involvement of the liver, skin, and lower GI tract. All cases of lower-GI involvement were limited to stage 1. Therefore, at least in the context of this study, this intervention appeared safe. There were no excess infections. The limited data from these 24 patients suggested that the efficacy was fairly promising. A larger, randomized phase 3 study comparing this strategy against a standard prophylactic regimen will be needed to confirm whether it provides any incremental value.

A study from Germany evaluated the genetic risk of severe chronic GVHD defined by host-derived C-X-C motif chemokine receptor 3 (CXCR3) ligands.[11] Biomarkers are available for acute GVHD, but are more limited for chronic GVHD. It is an area of unmet need. The investigators performed genomic analysis of CXCR3 and its ligands: CXCL4, CXCL9, CXCL10, and CXCL11. They also measured the cytokines associated with this pathway. At their center in Germany, prophylaxis involves a statin-based endothelial approach. Previous data suggested that statins can decrease the risk of chronic GVHD.[12] The study had 2 cohorts: the statin-based endothelial protection (SEP) cohort, with 287 patients, and the no-SEP cohort, with 401 patients. They interrogated these 2 data sets with genomic analyses of the candidate genes and their ligands, as outlined above.

An episode of GVHD was reported in 50 of 287 patients in the no-SEP cohort, 53 of 401 patients in the SEP cohort, and 14 of 202 patients in the no-SEP validation cohort. A genetic analysis identified a single-nucleotide polymorphism (SNP) in

the CXCL9/11 locus that appeared to be associated with severe chronic GVHD. This SNP is denoted by the name rs884304. Based on this classic association analysis, the investigators concluded that, taken together, high-risk patients can be identified in these 3 cohorts. Patients in the high-risk group had significantly higher serum levels of CXCL9 at day 28 and a significantly higher risk of severe GVHD. The investigators also developed a combined score, which consisted of both the SNPs and the protein levels, which provided a high-risk/low-risk model showing that the cumulative incidence of chronic GVHD could be predicted by this approach.

Independent validation for this approach is needed from another center. A limitation to this study is that it did not use a false discovery rate. When doing these types of multiple analyses, a concept called false discovery rate must be applied to assure statistical robustness. Corrections may be needed to statistically adjust for multiple testing.

A study from Canada found that high exposure to thymoglobulin before hematopoietic cell transplant was associated with a low risk of relapse.[13] Thymoglobulin is given as part of the conditioning regimen to prevent acute and chronic GVHD. The target of thymoglobulin is the host immune system, as well as the donor immune system. Thymoglobulin is dosed according to the recipient's body weight. The optimal dose is unclear because the targets are both the host and the donor, and the host's weight has nothing to do with the donor's immune-system repertoire that is being transplanted. The scientific community has therefore struggled with when to administer thymoglobulin and how much is needed. This study used pharmacodynamic profiling of the thymoglobulin area under the curve (AUC), separating it into pretransplant AUC and post-transplant AUC. They found that high pretransplant AUC appears to result in a lower rate of relapse. Now, it is also known that thymoglobulin by itself can kill leukemia, but that is not the primary effect. The primary effect is immunosuppression. The researchers postulated that a higher dose level before transplant corresponds to better protection and relapse because thymoglobulin works against leukemia. A higher dose after transplant leads to a low incidence of GVHD, but it then abrogates the graft-vs-tumor effect, leading to a higher incidence of relapse of the underlying disease.

This study adds to the body of literature highlighting the need for smarter ways of dosing thymoglobulin. There is still no optimal approach. It is not known whether the timing and dosing of thymoglobulin can control the pretransplant and post-transplant AUC.

Disclosure

Dr Jagasia has received research funding from Mallinckrodt and Janssen. He is an advisory board member/consultant for Incyte and Kadmon.

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NOTES

The Steroid-dependent aGVHD Patient

Advances in graft-versus-host disease (GVHD) prophylaxis regimens have expanded the donor pool for allogeneic hematopoietic stem cell transplantation and improved patient outcomes.[1] Despite this progress, acute GVHD (aGVHD) remains one of the major challenges to successful transplant outcomes.[2]

Systemic corticosteroids (CS) have remained the standard of care for aGVHD for over 3 decades; however, less than half of patients will achieve a durable response. Long-term mortality rates for patients who do not respond to CS are estimated at 80% or higher.[3,4]

There are 2 aGVHD patient groups for which CS fail to produce an adequate response (Figure).

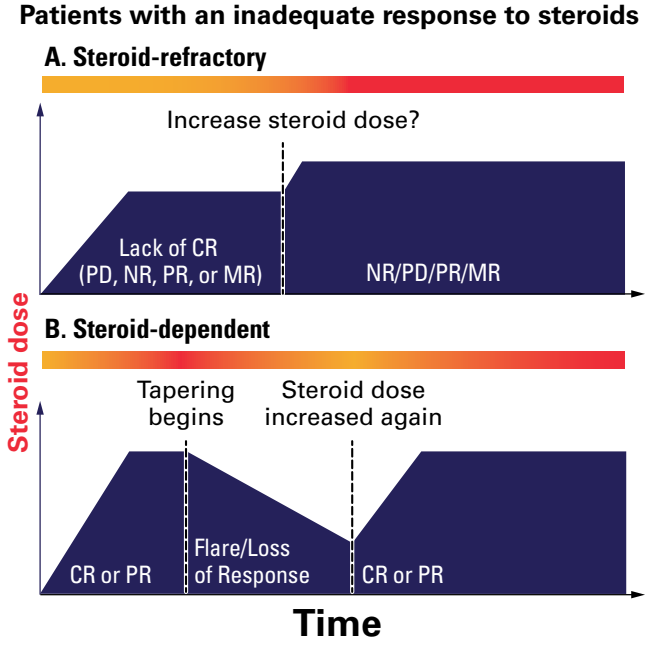

Figure. **A.** Steroid-refractory patients are those who progress or fail to improve following steroid treatment **B.** Steroid-dependent patients are those that cannot taper without flaring

Steroid-refractory or steroid-resistant (SR) aGVHD refers to worsening of aGVHD symptoms or failure to improve despite treatment with high-dose CS (Fig A).[4,5]

The American Society of Blood and Marrow Transplantation suggests that a patient be considered SR after 3 days with worsening disease manifestations of aGVHD, 1 week with ongoing grade 3 aGVHD and no improvement, or 2 weeks with ongoing grade 2 aGVHD and no improvement.[5]

Patients with steroid-dependent (SD) aGVHD are initial responders unable to taper/discontinue steroids without a return of symptoms (Fig B).[4]

Patients who are SD have not been well studied in the literature, are often excluded from clinical studies of secondary therapy for aGVHD, and have been defined inconsistently in trial inclusion criteria.[6-9]

Both SD and SR aGVHD patients face an array of potentially serious toxicities due to cumulative CS exposure.[10,11] The risk of several CS-related side effects, including infection, myopathy, and psychiatric disorders, is elevated within weeks to months of initiating treatment.[10,11] CS may also compromise the beneficial graft-versus-leukemia (GVL) effect mediated by donor lymphocytes, increasing risk of relapse.[12]

Outcomes for patients who are SD are sometimes considered more favorable than those for patients who are SR.[4,8] However, few studies have directly compared outcomes for SR and SD patients. In 2 studies that reported such data, 2-year outcomes such as overall survival and nonrelapse mortality appeared similar.[6,13]

Increasing evidence suggests that both SR and SD aGVHD patients are inadequate responders and should be managed to minimize exposure to CS and improve patient outcomes.

Increasing evidence suggests that both SR and SD aGVHD patients are inadequate responders and should be managed to minimize exposure to CS and improve patient outcomes.

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