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Regular Article



CLINICAL TRIALS AND OBSERVATIONS

# Effective treatment of low-risk acute GVHD with itacitinib monotherapy

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**KEY POINTS**

- **Itacitinib monotherapy is as effective as systemic corticosteroids for the treatment of low-risk acute GVHD.**
- **Itacitinib monotherapy resulted in fewer serious infections compared with systemic corticosteroids.**

**The standard primary treatment for acute graft-versus-host disease (GVHD) requires prolonged, high-dose systemic corticosteroids (SCSs) that delay reconstitution of the immune system. We used validated clinical and biomarker staging criteria to identify a group of patients with low-risk (LR) GVHD that is very likely to respond to SCS. We hypothesized that itacitinib, a selective JAK1 inhibitor, would effectively treat LR GVHD without SCS. We treated 70 patients with LR GVHD in a multicenter, phase 2 trial (NCT03846479) with 28 days of itacitinib 200 mg/d (responders could receive a second 28-day cycle), and we compared their outcomes to those of 140 contemporaneous, matched control patients treated with SCSs. More patients responded to itacitinib within 7 days (81% vs 66%, *P* = .02), and response rates at day 28 were very high for both groups (89% vs 86%, *P* = .67), with few symptomatic flares (11% vs 12%, *P* = .88). Fewer itacitinib-treated patients developed a serious infection within 90 days (27% vs 42%, *P* = .04) due to fewer viral and fungal infections. Grade ≥3 cytopenias were similar between groups except for less severe leukopenia with itacitinib (16% vs 31%, *P* = .02). No other grade ≥3 adverse events occurred in >10% of itacitinib-treated patients. There were no significant differences between groups at 1 year for nonrelapse mortality (4% vs 11%, *P* = .21), relapse (18% vs 21%, *P* = .64), chronic GVHD (28% vs 33%, *P* = .33), or survival (88% vs 80%, *P* = .11). Itacitinib monotherapy seems to be a safe and effective alternative to SCS treatment for LR GVHD and deserves further investigation.**

## Introduction

The primary treatment of acute graft-versus-host disease (GVHD), the principal morbidity associated with allogeneic transplantation, is systemic corticosteroids (SCS).[1,2] Systemic steroids themselves can lead to a number of morbidities, including hyperglycemia,[3] hypertension,[4] osteonecrosis,[5] and reduced quality of life.[6,7] Systemic steroids are also known to increase the risk of serious infections, including bacteremia and sepsis,[8,9] viral diseases such as cytomegalovirus (CMV)[10,11] and Epstein-Barr virus (EBV),[11] and invasive fungal infections.[11,12]

Treatment of acute GVHD with SCS usually lasts several months even when they cause complete resolution of GVHD symptoms.[2] Patients who present with less severe GVHD may therefore be at risk for overtreatment with steroids and consequent steroid-related morbidities.

Clinical and biomarker grading systems can identify GVHD patients who may benefit from reduced SCS treatment. The Minnesota classification system is based on GVHD symptom severity at diagnosis, and stratifies patients into 2 groups, namely, standard risk and high risk, with significantly different

risks for nonrelapse mortality (NRM).[13] The Mount Sinai Acute GVHD International Consortium (MAGIC) algorithm probability uses serum biomarker concentrations of ST2 and REG3α to categorize patients into 3 risk groups: low (Ann Arbor 1), intermediate (Ann Arbor 2), and high (Ann Arbor 3).[14,15] An analysis of 642 patients in the MAGIC database and biorepository showed that a combination of Minnesota standard risk and Ann Arbor 1 criteria identified a group of low-risk patients (~50% of all GVHD) with a 12-month NRM of ~10% (unpublished data).

Ruxolitinib, a JAK1/2 inhibitor, is approved by the US Food and Drug Administration as treatment for steroid-refractory (SR) acute GVHD.[16] Inhibition of the JAK-STAT pathway prevents activation of effector donor T cells that damage GVHD target organs.[17,18] We hypothesized that patients with low-risk acute GVHD could be effectively treated with a JAK inhibitor alone and therefore could avoid the morbid side effects of SCS. Although ruxolitinib is effective treatment for SR GVHD, we did not favor use of ruxolitinib in a low-risk setting because of significant myelosuppression and cytopenias that develop in one-third of patients.[16] We therefore chose to evaluate itacitinib, a more selective JAK1 inhibitor that had the potential to avoid such hematologic toxicities. In a recent randomized, phase III trial of itacitinib vs placebo in addition to SCS as primary treatment of GVHD, itacitinib was well tolerated and had a favorable safety profile without increased cytopenias even though it did not significantly increase the overall response rate (ORR) of acute GVHD symptoms compared with placebo.[19]

We hypothesized that itacitinib monotherapy would prove to be a safe and effective primary treatment for low-risk GVHD as determined by both clinical and biomarker criteria. We tested this hypothesis in a multicenter, phase II trial of 70 patients, and we compared key outcomes with those of a contemporaneous control cohort of 140 patients with low-risk GVHD from the MAGIC database and biorepository who received primary treatment with standard-of-care SCS.

# Methods

## Study design

We conducted a multicenter, phase II trial of itacitinib monotherapy between February 2019 and April 2021 for patients with previously untreated acute GVHD who were at low risk for resistance to treatment and NRM as defined by both clinical criteria (Minnesota standard risk)[13] and biomarker criteria (Ann Arbor 1).[14] Patients were aged 12 years and older and were required to have an absolute neutrophil count (ANC) ≥500/μL and a platelet count sustainable above 20 000/μL. Growth factor use and transfusion support were permitted. Exclusion criteria included uncontrolled infections; kidney, liver, or lung dysfunction; chronic GVHD; relapse of malignancy requiring discontinuation of immunosuppression; and treatment with a JAK inhibitor. There were no exclusions for donor type, human leukocyte antigen (HLA) match, stem cell source, conditioning regimen, or GVHD prophylaxis regimen. Patients could continue to receive immunosuppressants that were prescribed for GVHD prophylaxis, but initiation of new systemic immunosuppressants was not allowed. A sample size of 70 patients was selected to demonstrate a minimum ORR to itacitinib monotherapy of at least 52% compared with the historical response rate to SCS of 67% for low-risk patients within the MAGIC database (data not shown). The study was approved by the institutional review board at each center and was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent. The trial was registered with clinicaltrials.gov (NCT03846479).

## Study procedures

**Screening and enrollment** Patients who met clinical eligibility criteria had 5 mL of serum collected and shipped overnight to the MAGIC research laboratory for biomarker screening at the Tisch Cancer Institute. The MAGIC algorithm probability was determined and corresponding Ann Arbor scores calculated according to published methods.[14,15,20] Results were provided to the site within 30 hours of shipment. Patients who did not meet all inclusion and exclusion criteria were deemed screen failures and treated using the best available therapy according to physician discretion. A 4-day delay to the start of study treatment following determination of eligibility was allowed to accommodate outpatient evaluation and monitoring. Participating centers are listed in supplemental Table 1, available on the *Blood* website.

**Treatment** Study treatment consisted of oral administration of itacitinib 200 mg daily for 28 days, with a second 28-day cycle allowed for responding patients. Itacitinib was then discontinued without tapering. Topical (skin and enteric) treatments for GVHD were permitted and GVHD prophylaxis continued during treatment according to institutional protocols. All patients were required to receive antiviral, antifungal, and anti–*Pneumocystis jiroveci* prophylaxis. Monitoring for CMV and EBV viremia was required and performed according to institutional standards of practice. Up to 5 doses of itacitinib could be missed for nausea, difficulty swallowing, or other non–treatment-related complications, and missed doses were to be completed at the end of the cycle. Dose modifications were not allowed. Coadministration with strong CYP3A4 inhibitors was permitted, but patients were instructed to avoid foods that inhibited CYP3A4. Reasons for removal from treatment included the following: (1) worsening of GVHD within 3 days; (2) failure of GVHD to respond within 7 days if grade III or 14 days if grade II; (3) physician discretion; (4) withdrawal of consent; and (5) nonadherence to the treatment regimen. Patients removed from treatment for GVHD progression or lack of response were required to start prednisone ≥1 mg/kg per day or equivalent as salvage therapy. GVHD treatment for patients who stopped treatment for other reasons was at the discretion of the treating physician.

**Clinical data collection** GVHD grading and staging were performed according to previously published MAGIC guidance.[21] Clinical evaluation and GVHD staging were conducted at screening, weekly for 8 weeks, and less frequently thereafter until study day 365. All adverse events of grade 3 or higher were reported, regardless of relatedness to study drug according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4. Serious infections were reported through study day 90.

**Control cohort** Prior analysis of the MAGIC database and biorepository showed a 57% incidence of serious infections

## Table 1. Patient and transplant characteristics

| | Itacitinib (n = 70) | Systemic corticosteroids (n = 140) | *P* value* |
|---|---|---|---|
| Age at BMT, median [range] | 60 [15-74] | 59 [12-79] | .72 |
| **Indication for HCT, n (%)** | | | .07 |
| Acute leukemia | 32 (46%) | 75 (54%) | |
| Lymphoma | 6 (9%) | 13 (9%) | |
| MDS/MPN | 29 (41%) | 38 (27%) | |
| Nonmalignant | 3 (4%) | 5 (4%) | |
| Other malignant† | 0 (0%) | 9 (6%) | |
| **Donor type, n (%)** | | | .66 |
| Related | 28 (40%) | 61 (44%) | |
| Unrelated | 42 (60%) | 79 (56%) | |
| **Stem cell source, n (%)** | | | .08 |
| Bone marrow | 10 (14%) | 35 (25%) | |
| Peripheral blood | 60 (86%) | 105 (75%) | |
| **HLA match, n (%)** | | | .50 |
| Matched | 50 (71%) | 90 (64%) | |
| Mismatched | 5 (8%) | 17 (12%) | |
| Haploidentical | 15 (21%) | 33 (24%) | |
| **Conditioning intensity, n (%)** | | | .88 |
| Myeloablative | 33 (47%) | 68 (49%) | |
| Non-myeloablative/ reduced intensity | 37 (53%) | 72 (51%) | |
| **GVHD serotherapy, n (%)** | | | .19 |
| ATG | 9 (13%) | 29 (21%) | |
| No ATG | 61 (87%) | 111 (79%) | |
| **GVHD prophylaxis, n (%)** | | | .17 |
| CNI based | 33 (47%) | 82 (59%) | |
| Cyclophosphamide based | 35 (50%) | 55 (39%) | |
| T-cell depletion | 2 (3%) | 1 (1%) | |
| Sirolimus based | 0 (0%) | 2 (1%) | |
| **GVHD grade, n (%)** | | | .87 |
| Grade I | 12 (17%) | 25 (18%) | |
| Grade II | 55 (79%) | 111 (79%) | |
| Grade III | 3 (4%) | 4 (3%) | |
| **Target organ involvement, n (%)** | | | 1 |
| LGI ± other | 21 (30%) | 42 (30%) | |
| Skin 1/2 ± UGI | 16 (23%) | 30 (21%) | |
| Skin 3 ± UGI | 28 (40%) | 56 (40%) | |
| UGI only | 5 (7%) | 12 (9%) | |
| Histopathologic confirmation of GVHD | 35 (50%) | 54 (39%) | .14 |
| MAP median [range] | 0.064 [0.013-0.139] | 0.072 [0.020-0.140] | .08 |
| **CMV-seropositive donor or recipient** | | | .12 |
| Yes | 55 (79%) | 92 (66%) | |
| No | 15 (21%) | 47 (33%) | |
| N/A | 0 | 1 (1%) | |
| **Topical corticosteroids, n (%)** | | | .76 |
| Yes | 43 (61%) | 89 (64%) | |
| No | 27 (39%) | 51 (36%) | |

ATG, anti-thymocyte globulin; CNI, calcineurin inhibitor; CMV, cytomegalovirus; LGI, lower gastrointestinal; MAP, MAGIC algorithm probability; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; N/A, not available; UGI, upper gastrointestinal.

**P* values were obtained from the Fisher exact test for categorical variables and the Wilcoxon test for continuous variables.

†Other malignant: multiple myeloma (7), prolymphocytic leukemia (1), chronic lymphocytic leukemia (1).

within 90 days of treatment with SCS in patients with newly diagnosed Minnesota standard risk, Ann Arbor 1 acute GVHD compared to 28% in patients who were not treated with SCS ($P < .001$) (supplemental Figure 1). Patients treated with SCS also experienced a higher rate of infections per patient than the 69 patients treated without SCS (rate ratio, 2.39; 95% confidence interval [CI], 1.57-3.77]). For purposes of trial design, we postulated a lower incidence of serious infections (52%) in more contemporary patients due to advances in anti-infective supportive care, and determined that 140 controls would provide 80% power to detect a 50% reduction in serious infections (52%-26%) compared to 70 trial patients. When accrual to the trial was complete, we identified a cohort of 140 control patients from the MAGIC database and biorepository, which includes prospectively collected clinical data and serum samples from patients enrolled on a natural history trial of acute GVHD. This observational trial uses a rigorous PRoBE design,[22] and is institutional review board approved at each center. These 140 patients underwent transplantation between January 2015 and March 2021, and met all the inclusion and exclusion criteria for the study. Control patients received a minimum of 0.5 mg/kg per day of prednisone equivalent with a mean starting dose of 1.28 ± 0.05 mg/kg. Matching was performed at the group level with prioritization given to target organ stage, GVHD prophylaxis regimen, HLA match, and donor type using the Mahalanobis distance optimal matching method (MatchIt R package).[23-25] These patients were closely matched to the study population for all key characteristics (Table 1), and the control cohort met the validity and reliability criteria for comparative analyses recommended by the US Food and Drug Administration and the European Medical Agency.[26] Centers that provided control patients are listed in supplemental Table 1.

## End points and statistical methods

The primary end point was the ORR at 28 days of treatment, defined as the proportion of patients achieving either a

complete response (CR) or a partial response (PR) of GVHD symptoms without the addition of other systemic therapy. PR was defined as an improvement in 1 or more affected organs without worsening in others.

Secondary end points included the number of treatment emergent adverse events (TEAEs) that were grade 3 or higher; the number and incidence of serious infections through day 90, as defined by clinically significant infection requiring systemic treatment; the cumulative incidence at 12 months of relapse, chronic GVHD (cGVHD), and NRM; and overall survival at 12 months. TEAEs occurring after relapse were not counted. A second infection with the same organism was considered a new infection if the interval between episodes met criteria defined by the Blood and Marrow Transplant Clinical Trials Network (eg, 7 days for bacterial infections).[27] Fevers of unknown origin were not counted as clinically significant infections even if treated with systemic antibiotics. NRM was defined as death after allogeneic hematopoietic cell transplantation (HCT) not attributed to relapse of the underlying disease. Relapse or second transplant were considered competing risks for NRM; death was a competing risk for relapse; and relapse or death were competing risks for chronic GVHD.

Additional secondary end points included the proportion of patients who developed maximum grade III/IV GVHD, treatment-resistant GVHD, and flares of acute GVHD after an initial response. Treatment resistance was defined as lack of CR or PR by day 28 of treatment or the start of additional treatment before day 28. GVHD flares were defined as an increase in GVHD symptoms after an initial response that required the resumption of, or increase in, systemic steroid dose of at least 10 mg/d, or the initiation of another systemic treatment. The cumulative steroid dose in milligrams per kilogram of prednisone equivalent by day 56 of systemic treatment was calculated using the weekly steroid dose without adjustment of the observation period for competing risks.

Differences between groups were compared via the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Cumulative incidence analyses were conducted via the Fine and Gray method,[28] and cumulative incidence curves were compared using the Gray test.[29] Kaplan-Meier survival curves were compared using the log-rank test.[30] A Poisson regression analysis was used to compare the number of infections experienced per patient.[31] Because patients could experience more than 1 infection, a generalized linear mixed model[32] was used to estimate the odds ratio (OR) for the severity of infections by cohort. All tests were 2 sided; a $P$ value of <.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute).

# Results

## Study patients

A total of 88 patients with Minnesota standard risk GVHD were screened for this trial. Ten patients (11%) were ineligible because of an Ann Arbor score >1, and the remaining 78 patients with Minnesota standard risk and Ann Arbor 1 GVHD were eligible for treatment. Six eligible patients did not enroll because of physician discretion. Two patients who enrolled were removed from treatment and replaced, 1 patient for an alternative histologic diagnosis on a pretreatment biopsy and 1 patient for noncompliance. Neither experienced treatment-related adverse events, and both were excluded from further analyses.

## Patient characteristics

A total of 70 patients who met all inclusion and exclusion criteria were treated with itacitinib alone as primary treatment for acute GVHD (Table 1). We identified a population of 140 controls with similar GVHD presentation and pretransplantation variables who received SCSs as primary treatment (Table 1). There were no significant differences between the 2 cohorts for any key variables, and 30% of patients in each group presented with lower gastrointestinal (GI) symptoms. The groups were also well balanced for continued use of GVHD immunosuppressive agents at the start of systemic treatment (supplemental Table 2). The median day of systemic treatment initiation following HCT was 11 days later in the trial patients than in the control patients (46 vs 35 days, $P$ = .001). The distribution of timing of itacitinib initiation from screening is detailed in supplemental Table 3.

## GVHD outcomes

Both groups showed excellent ORR at day 28: 89% (62/70) for itacitinib alone and 86% (120/140) for SCS ($P$ = .67) (Figure 1A). ORR in the 30% of patients presenting with lower GI symptoms in each group was also excellent (86% for both groups, $P$ = 1) (Figure 1B). There were no significant differences in ORR between any subgroups when analyzed by presenting GVHD grade, target organ involvement, pretransplantation characteristics, or GVHD prophylaxis, including posttransplantation cyclophosphamide, or number of days post-HCT of treatment initiation (Table 2). For 63 trial patients, the grade of GVHD remained the same between screening and treatment initiation; in 2 patients, the grade of GVHD increased; and in 5 patients, the grade decreased in this interval. However, this had no effect on the ORR because, in all 7 patients, response at day 28 remained the same regardless of whether the staging measured at screening or at the first day of itacitinib treatment was used as the baseline. Furthermore, the ORR was the same whether

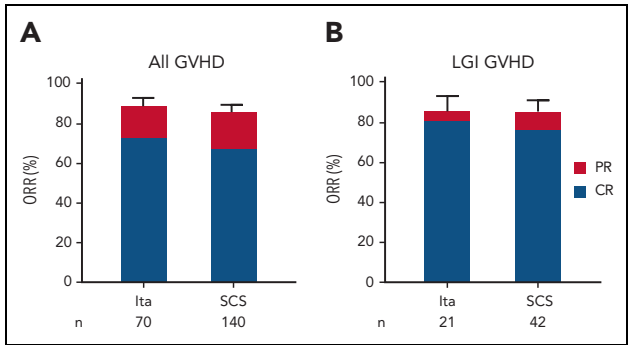


**Figure 1. ORR after 4 weeks of systemic therapy for GVHD.** ORR was defined as CR and PR within 28 days of treatment with either itacitinib (Ita) or systemic corticosteroids (SCS) without additional therapy. (A) All GVHD patients. (B) Patients with lower GI (LGI) symptoms.

**Table 2. ORR stratified by GVHD and patient characteristics**

| | Itacitinib (n = 70) | Systemic corticosteroids (n = 140) | *P* value |
|---|---|---|---|
| **GVHD characteristics** | | | |
| GVHD grade | | | |
| Grade I | 11/12 (92%) | 19/25 (76%) | .39 |
| Grade II/III | 51/58 (90%) | 101/115 (88%) | 1 |
| Target organ involvement | | | |
| LGI ± Other | 18/21 (86%) | 36/42 (86%) | 1 |
| Skin 1/2 ± UGI | 15/16 (94%) | 24/30 (80%) | .39 |
| Skin 3 ± UGI | 26/28 (93%) | 51/56 (91%) | 1 |
| UGI Only | 3/5 (60%) | 9/12 (75%) | .60 |
| Days between HCT and start of systemic treatment* | | | |
| ≤40 | 23/26 (88%) | 73/85 (86%) | 1 |
| >40 | 39/44 (89%) | 47/55 (85%) | .77 |
| **Patient characteristics** | | | |
| Age, y | | | |
| <60 | 31/34 (91%) | 66/77 (86%) | .55 |
| ≥60 | 31/36 (86%) | 54/63 (86%) | 1 |
| Donor type | | | |
| Related | 23/28 (82%) | 53/61 (87%) | .54 |
| Unrelated | 39/42 (93%) | 67/79 (85%) | .26 |
| Stem cell source | | | |
| Bone marrow | 10/10 (100%) | 33/35 (94%) | 1 |
| Peripheral blood | 52/60 (87%) | 87/105 (83%) | .66 |
| HLA match | | | |
| Matched | 44/50 (88%) | 77/90 (86%) | .80 |
| Mismatched | 4/5 (80%) | 15/17 (88%) | 1 |
| Haploidentical | 14/15 (93%) | 28/33 (85%) | .65 |
| Conditioning intensity | | | |
| Myeloablative | 29/33 (88%) | 59/68 (87%) | 1 |
| Non-myeloablative/ reduced intensity | 33/37 (89%) | 61/72 (85%) | .77 |
| GVHD prophylaxis | | | |
| CNI based | 29/33 (88%) | 71/82 (87%) | 1 |
| Cyclophosphamide based | 32/35 (91%) | 47/55 (85%) | .52 |
| Other | 1/2 (50%) | 2/3 (67%) | 1 |

Denominators reflect the number of patients within each subgroup of each GVHD or patient characteristic. Numerators reflect the number of patients who had a complete response (CR) or partial response (PR) to treatment within each subgroup.

HCT, hematopoietic cell transplantation; LGI, lower gastrointestinal; UGI, upper gastrointestinal.

*The median number of days from HCT to start of systemic treatment for the entire cohort (n = 210) was 40 days.

patients started itacitinib ≤2 days or >2 days from screening (28/31, 90% vs 34/39, 87%, *P* = 1).

Significantly more patients treated with itacitinib achieved a response by day 7 compared with patients treated with SCS (81% vs 66%, *P* = .02), and responses were equally durable up to day 90 in both groups (55/62, 89% vs 106/120, 88%; *P* = 1). Among responding patients, durable responses were as likely in those who received only the first month of itacitinib (8/9, 89%) and in those who received up to 2 months of itacitinib (47/53, 89%). There were no significant differences in the rates of maximum grade III/IV GVHD, GVHD resistant to 28 days of primary therapy, or GVHD flares within 90 days of initial systemic GVHD treatment (Table 3). No baseline characteristics predicted resistance to treatment either with itacitinib or with SCS (supplemental Tables 4 and 5). Seven of 8 patients whose GVHD was resistant to itacitinib were successfully salvaged with SCS. An additional 7 patients received SCS for treatment of a GVHD flare prior to day 90, and thus 55 of 70 (79%) trial patients did not require any SCS for treatment of acute GVHD. As expected, the mean cumulative steroid dose was minimal in trial patients; control patients treated with SCS received mean cumulative doses consistent with published guidance (Table 3).[1] As shown in Figure 2, there were no significant differences between trial and control patients in the 12-month cumulative incidence of relapse (18% vs 21%, *P* = .64), chronic GVHD (28% vs 33%, *P* = .33), or NRM (4% vs 11%, *P* = .21). Similarly, the survival at 12 months was similar between trial and control patients (88% vs 80%, *P* = .11).

## Safety

In all, 86% of patients (n = 60) completed the first 28-day cycle of itacitinib treatment, and 61% (n = 43) completed the second 28-day cycle. Of the patients, 10% (n = 7) discontinued itacitinib because of lack of efficacy, and 29% (n = 20) discontinued the drug because of TEAEs (n = 18) or relapse of malignancy (n = 2) (supplemental Table 6). Four patients discontinued treatment because of TEAEs during the first cycle at a median of 15 days (range, 11-21 days). Two of these patients who had already responded to itacitinib maintained their response at the assessment of the primary end point. An additional 14 patients did not complete the second cycle due to TEAEs after receiving treatment for a median of 35 days (range, 27-45 days). One of these patients required SCS for a GVHD flare 2 weeks after discontinuation of itacitinib. Hematologic adverse events were the most common reason for discontinuation of itacitinib (n = 14). Comparison of trial and control patients showed no differences in grade ≥3 cytopenias through 90 days, with the exception of less leukopenia in patients treated with itacitinib (16% vs 31%, *P* = .02). All grade ≥3 cytopenias are listed in Table 4. All nonhematologic, noninfectious TEAEs in itacitinib-treated patients are listed in Table 5.

## Serious infections

The incidence, number, and severity of infectious complications, a key secondary end point, were lower in trial patients than in control patients when analyzed by 3 separate metrics. First, the cumulative incidence of patients with at least 1 serious infection within 90 days of treatment was significantly lower after itacitinib treatment than after SCS treatment (Figure 3A), resulting from fewer viral and fungal infections in the itacitinib group (Figure 3B). Second, the mean number of infections per patient was lower in the itacitinib group compared to the SCS group (0.43 vs 0.66, *P* = .04), with a corresponding rate ratio of 0.65 (95% CI, 0.43-0.97). Third, trial patients were less likely to develop a severe (Blood and Marrow Transplant Clinical Trials Network [BMT CTN] grade 2 or 3) infection than control patients (OR, 0.50 [95% CI, 0.27-0.93]). Although more trial patients received letermovir for CMV prophylaxis than did

## Table 3. Additional GVHD outcomes

| | Itacitinib (n = 70) | Systemic corticosteroids (n = 140) | *P* value |
|---|---|---|---|
| Maximum grade III/IV GVHD (n, %) | 6 (9%) | 15 (11%) | .81 |
| GVHD resistant to primary treatment through day 28 (n, %) | 8 (11%) | 20 (14%) | .67 |
| Flares (n, %)* | 7 (11%) | 14 (12%) | .88 |
| Cumulative prednisone dose (mg/kg) through day 28 (mean ± SEM) | 1.9 ± 0.6 | 22.0 ± 1.0 | <.001 |
| Cumulative prednisone dose (mg/kg) through day 56 (mean ± SEM) | 3.7 ± 1.2 | 30.0 ± 1.5 | <.001 |

Outcomes were monitored for 90 days unless otherwise stated. Flares of GVHD and GVHD resistant to primary treatment are defined as in "Methods."

*Flares are calculated among the subset of patients with a CR/PR after 28 days of systemic therapy without additional therapy: itacitinib (n = 62); SCS (n = 120).

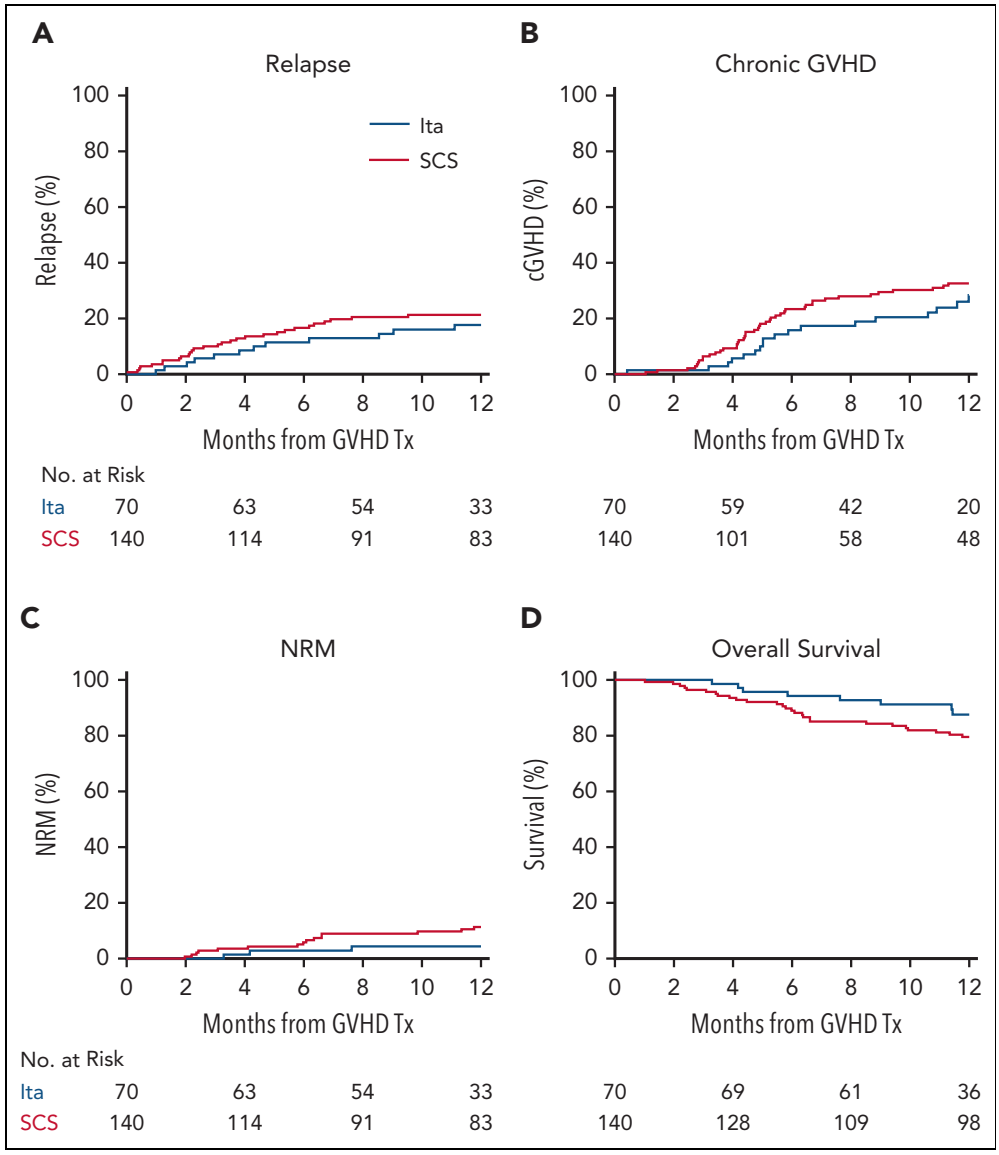


**Figure 2. Long-term outcomes following systemic treatment of acute GVHD.** *P* values express the difference between the itacitinib (Ita) and the systemic corticosteroid (SCS) groups. The Gray test was used to compare cumulative incidences, and the log-rank test was used to compare survival between groups. (A) Relapse: *P* = .64. (B) cGVHD: *P* = .33. (C) NRM: *P* = .21. (D) Overall survival (OS): *P* = .11.

**Table 4. New or worsening grade 3 or 4 cytopenias through 10 weeks of systemic treatment**

| | Itacitinib (n = 70) | Systemic corticosteroids (n = 140) | *P* value |
|---|---|---|---|
| Leukopenia | 11 (16%) | 44 (31%) | .02 |
| Anemia | 14 (20%) | 25 (18%) | .71 |
| Thrombocytopenia | 13 (19%) | 39 (28%) | .18 |
| Neutropenia | 11 (16%) | 32 (23%) | .28 |
| Any cytopenia | 26 (37%) | 69 (49%) | .11 |

Data are for patients who developed a new grade 3 or 4 cytopenia or a baseline grade 3 cytopenia that progressed to grade 4.

control patients (53% vs 10%, $P < .001$), its use was not associated with significantly fewer infections (OR, 0.64 [95% CI, 0.32-1.26]) or serious CMV infections (OR, 0.39 [95% CI, 0.14-1.04]). However, the development of severe leukopenia after initiation of GVHD treatment was a significant predictor for subsequent serious infections (OR, 2.08 [95% CI, 1.05-4.09]). All serious infections are listed in supplemental Table 7.

## Discussion

We tested the hypothesis that itacitinib could safely replace SCS treatment in patients whose GVHD was expected to be highly responsive to treatment based on both clinical and biomarker criteria. Comparison of 70 itacitinib-treated patients to 140 closely matched, near-contemporaneous controls treated with SCS showed that both treatment approaches produced excellent clinical responses in all subgroups, including patients with lower-GI GVHD. Itacitinib produced significantly more responses within 7 days than SCS and, once achieved, responses were durable for both groups. Itacitinib treatment also appears to be associated with fewer serious infections. Furthermore, there was no difference in relapse, NRM, chronic GVHD, or survival between itacitinib and control patients in the first year following treatment. GVHD that did not respond to itacitinib responded to SCS, lending confidence to a strategy that reserves SCSsfor second-line treatment.

SCS therapy causes substantial toxicity, especially in immunocompromised populations. Itacitinib demonstrated a favorable safety profile with a low incidence of grade ≥3 nonhematologic and noninfectious TEAEs, and no event occurred in more than 10% of patients. Neutropenia, anemia, and thrombocytopenia, the major dose-limiting side effects of ruxolitinib,[16,33] developed at the same frequency in both itacitinib and control patients. This finding is consistent with the absence of itacitinib-induced myelosuppression compared with placebo in patients with moderate-to-severe GVHD.[19]

The 42% cumulative incidence of serious infections by day 90 in the control group is similar to the cumulative incidence reported for patients treated with SCS alone as primary treatment for standard-risk GVHD in a randomized, multicenter study.[7] Our data suggest that itacitinib may be safer than SCS because significantly fewer patients developed serious infections, particularly serious viral infections, during the first 28 days, a finding that could not be explained by greater use of letermovir for CMV prophylaxis in this group. Chronic SCS treatment is known to depress lymphocyte function,[34,35] and fewer infections in the itacitinib group may be related to the very large reduction (91%) in day 28 cumulative corticosteroid exposure. Less severe leukopenia may also have contributed to the lower incidence of serious infections in the itacitinib group.

Our findings must be interpreted cautiously, however, because the 2 groups were not randomized and we did not control for numerous other host and donor factors that may contribute to the risk of hematologic toxicities or infections. Prophylaxis for common infections in immunocompromised hosts was not standardized for either trial or control patients, which may also have affected infection risk. Furthermore, patients likely to respond to therapy can be overrepresented in GVHD studies, resulting in better outcomes than expected.[19,36,37] In this study, treatment for trial patients could be delayed for up to 4 days, potentially selecting for a very low-risk patient population; however, we note that patients who delayed initiation of itacitinib (>48 hours from screening) were no more likely to respond to treatment than those who started treatment promptly. In addition, 17% of the patients in this study were treated for grade I GVHD. A recent publication found that approximately 50% of patients with grade I GVHD assigned to an observation-only arm never required systemic treatment.[38] A future study could test whether patients with grade I GVHD that is also Ann Arbor 1 by biomarkers can be successfully managed with topical treatment alone.

A recent randomized BMT CTN study of primary therapy for acute GVHD comparing sirolimus monotherapy to SCS[7] found no

**Table 5. Treatment emergent adverse events of grade ≥3 (nonhematologic, noninfectious)**

| Itacitinib (n = 70) | Grade 3 |
|---|---|
| Any | 21 (30%) |
| Alanine aminotransferase increased | 5 (7.1%) |
| Hypertension | 4 (5.7%) |
| Syncope | 2 (2.9%) |
| Hypertriglyceridemia | 1 (1.4%) |
| Posterior reversible leukoencephalopathy syndrome | 1 (1.4%) |
| Fall | 1 (1.4%) |
| Subarachnoid hemorrhage | 1 (1.4%) |
| Thrombotic microangiopathy | 1 (1.4%) |
| Hemorrhagic cystitis | 1 (1.4%) |
| Vomiting | 1 (1.4%) |
| Arthralgia and/or myalgia | 2 (2.9%) |
| Hypomagnesemia | 1 (1.4%) |

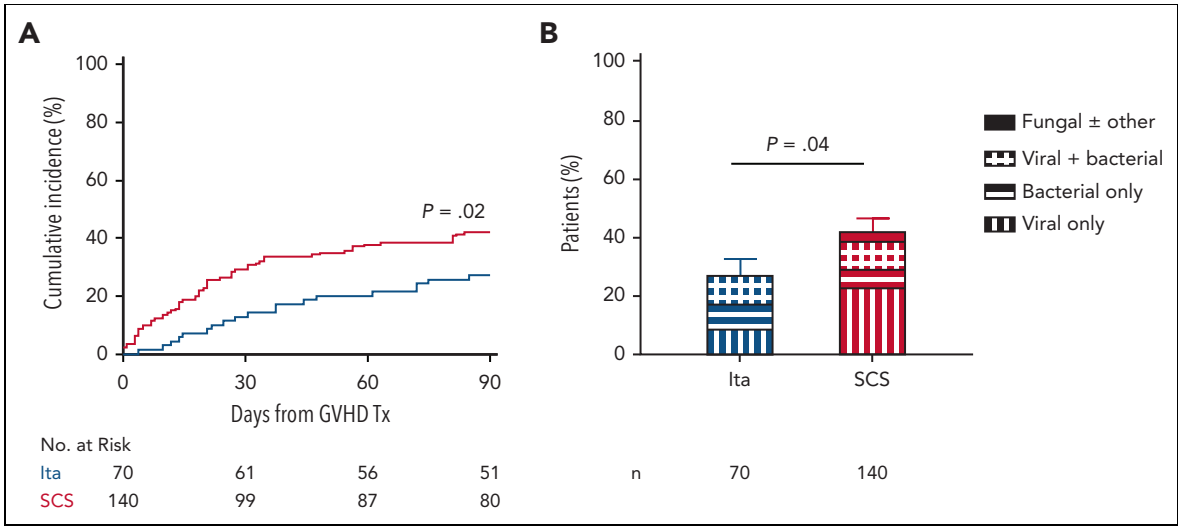


**Figure 3. Serious infections within 90 days following systemic treatment of acute GVHD.** *P* values express the difference between the itacitinib (Ita) and systemic corticosteroid (SCS) groups. The Gray test was used to compare cumulative incidences, and the Fisher exact test was used to compare categories of serious infections. (A) Cumulative incidence. (B) Categories of serious infections. Any patient with a fungal infection is included in fungal ± other. One control patient included in the viral + bacterial category also had a parasitic infection.

difference between arms in day 28 ORR (65% and 73%, respectively). However, sirolimus was associated with a greater than 10% incidence of transplant-associated microangiopathy, and there was no change in the incidence of serious infections. It should be noted that the higher response rates in both groups in the current study are likely due to the exclusion of higher-risk Ann Arbor 2 patients, who were included in the BMT CTN trial. Another recent randomized study failed to demonstrate higher response rates with the combination of itacitinib and high-dose SCS for acute GVHD, but this study likely included large numbers of patients with low-risk biomarkers who would be expected to respond to SCSs alone.[19]

In conclusion, a short course of itacitinib monotherapy was a safe and effective alternative to treatment with SCS for patients diagnosed with low-risk acute GVHD, a group that comprises approximately 50% of all GVHD patients receiving systemic treatment. Patients with low-risk GVHD are ideal for testing strategies that de-escalate treatment intensity, by either replacing SCS with less toxic drugs or using shorter SCS courses, or both. A randomized trial of itacitinib vs SCS is necessary to expand and validate these findings, and to determine the benefits of an SCS-free approach to GVHD treatment.

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## Authorship

Contribution: A.E., U.Ö., J.L.M.F., and J.E.L. conceived and designed the study; A.E., A.A., M.M.A.M., H.C., Z.D., W.J.H., C.L.K., F.A., J.B., I.G., S. Kasikis, S.G., E.H., M.H., U.K., A.L., M.M., M.Q., R.R., W.R., N.S., R.Y., and Y.-B.C. collected and reviewed the clinical data; A.C., S. Kowalyk, and G.M. performed the laboratory analysis; A.C., D.K., N.S., and U.Ö. performed the statistical analysis; A.E., A.C., J.L.M.F., and J.E.L. wrote the manuscript; and all authors contributed to the manuscript and approved the final version.

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## Footnotes

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For data sharing, please contact the corresponding author or aaron.etra@mountsinai.org.

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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