How I Treat:

When to Intervene With Jakafi® (ruxolitinib) in Patients With Chronic GVHD

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Chronic graft-versus-host disease (GVHD) is the primary cause of morbidity and non-relapse mortality after allogeneic hematopoietic cell transplantation. Because the trajectory of cGVHD can be rapid and unpredictable, my management goals for my patients with chronic GVHD are to arrest the development of chronic GVHD early on and prevent progression. I take a proactive and systematic approach to symptom assessment to identify early signs of systemic steroid failure. Timely diagnosis of steroid-refractory cGVHD and initiation of therapy are important to potentially minimize irreversible tissue damage. To achieve my treatment goals, and as supported by the REACH3 trial data and my real-world experience, I intervene early with Jakafi in appropriate patients at the first signs of initial systemic treatment failure.

Jakafi® (ruxolitinib) is indicated for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

Overview of cGVHD: Risk of Progression and Treatment Goals

Chronic GVHD is the primary cause of morbidity and non-relapse mortality after allogeneic hematopoietic cell transplantation.

cGVHD is mediated by donor immune cell attack on host tissue. Cytokine release leads to activation of the innate immune system, resulting in dysregulated T-cell immunity, B-cell activation, and fibroblast proliferation. As cGVHD progresses, ultimately fibrotic end-organ tissue damage may occur.[1] Patients may face the consequences of that outcome for the rest of their lives.

Because the trajectory of cGVHD can be rapid and unpredictable, my management goals for my patients with chronic GVHD are to arrest the development of chronic GVHD early on and prevent progression.

> **Like a biological point of no return, once the earlier stages of inflammation are missed, there is a chance that the tissue damage may become irreversible, and organ function cannot be regained.**

Early Recognition of Signs and Symptoms Through Systemic Assessment

Recognizing early signs and symptoms is the first step to intervention. During routine visits with my patients, I go system by system, top to bottom, in order not to miss anything.

Eyes, mouth, and skin round up the organs with the most common early signs or symptoms of chronic GVHD.

- Eyes: I look for new onset of dryness in eyes or changes in visual acuity. The eyes are easily overlooked by patients because they may not associate dry eyes with chronic GVHD.
- Mouth: I look for reports of dryness, new sores, sensitivity to normally tolerated foods and reduced mouth opening, or signs of dysphagia. I may ask, "Do you have to drink more water in order for food to go down?"
- Skin: I look for early signs, such as lichenoid changes, new patches of dry skin, tightness of the skin, or formation of lesions, which may present on their upper trunk, neck, and the posterior part of their torso.

Asking specific questions system by system is more productive than a general question about what might have changed. It's also important to discuss topics that are often stigmatized, such as sexual health. For example, I may ask:

- Lungs: "Are you able to speak a full sentence without stopping for breath?"
- Joints: "Do you feel any joint discomfort in the morning or tightness when you walk around?"
- Gastrointestinal: "Are there any changes in stool color or formation?"
- Genital: For male patients "Do you have normal morning erection?" For female patients, "Are you feeling any dryness or difference in vaginal moisturization?"
- Sexual health: "Are you able to have normal penetrative intercourse?" "Are you having any pain, discomfort, or bleeding after the penetrative intercourse?"

Patients also need to stay vigilant as they play a key role in recognizing signs and symptoms of cGVHD. In my practice, I tell my patients to track changes in symptoms in between their visits and call me when they experience any of their changes for more than a week.

> **Patient education on the early signs and symptoms of chronic GVHD, and how they evolve, should be a continuous effort, as the potential for chronic GVHD does not end at year 1 or 8, post transplant.**

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Diagnosis of Steroid-Refractory and Steroid-Dependent cGVHD

Timely diagnosis and initiation of therapy are important to potentially minimize irreversible tissue damage. I follow the NIH consensus criteria for steroid-refractory and steroid-dependent cGVHD in my practice.[2] For example, if a chronic GVHD patient presents with rash and is started on prednisone ≥1 mg/kg/day, I expect to see objective improvements during examination as well as subjective improvements in rash and discomfort within the first week.

In my experience, if I don't see at least some response within the first week of high-dose steroid initiation or I am unable to taper steroid use, I intervene with Jakafi® (ruxolitinib), as opposed to taking the chance that the disease could become more severe.

REACH3 Trial Data for Jakafi and My Approach for Early Intervention With Jakafi

My approach to steroid-refractory cGVHD is to intervene early with Jakafi at first signs of steroid-refractory cGVHD, based on the REACH3 trial data.[3]

REACH3 is a randomized, open-label, multicenter, phase 3 study of Jakafi vs best available therapy (BAT)*, in patients with steroid-refractory chronic GVHD (N=329).[3,4] The starting dose for Jakafi was 10 mg BID. Crossover from BAT to Jakafi was permitted on or after week 24 if patients progressed, had a mixed or unchanged response, developed toxicity to BAT, or experienced a cGVHD flare.[4]

REACH3 Primary Endpoint

At week 24, significantly more patients achieved a response with Jakafi compared with BAT, with an overall response rate (ORR) of 49.7% (82/165) compared with 25.6% (42/164) (OR, 2.99 [95% CI: 1.86, 4.80]; *P* < 0.0001).[4]

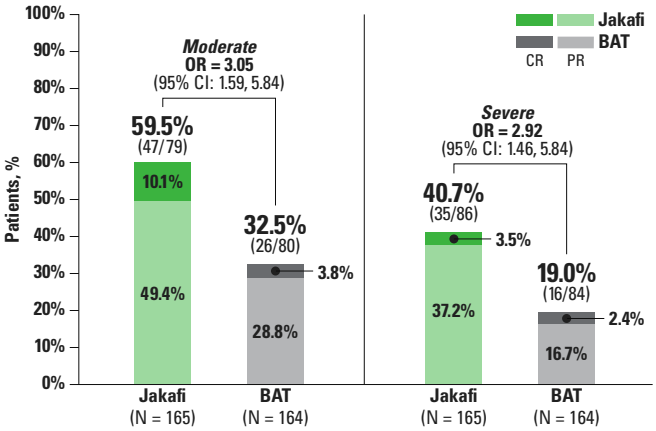
This higher response with Jakafi compared with BAT is also seen through week 24, with an ORR of 70% (116/165) vs 57% (94/164).[3]

Significance in the primary endpoint supports my choice of Jakafi in my steroid-refractory cGVHD patients. Additionally, subgroup analysis guides me on the timing of intervention and supports my approach of early intervention with Jakafi to achieve the most impact in my patients.

Regardless of baseline disease severity, overall response rates are higher in the Jakafi group compared with BAT at week 24. Within the Jakafi group, initiation of Jakafi in the moderate disease group is associated with higher overall response rate at 59.5% compared with 40.7% in severe disease group.[5] (Figure 1)

Figure 1

REACH3: Subgroup Analysis of Overall Response Rates by Baseline Disease Severity at Week 24[5,6,a,b]

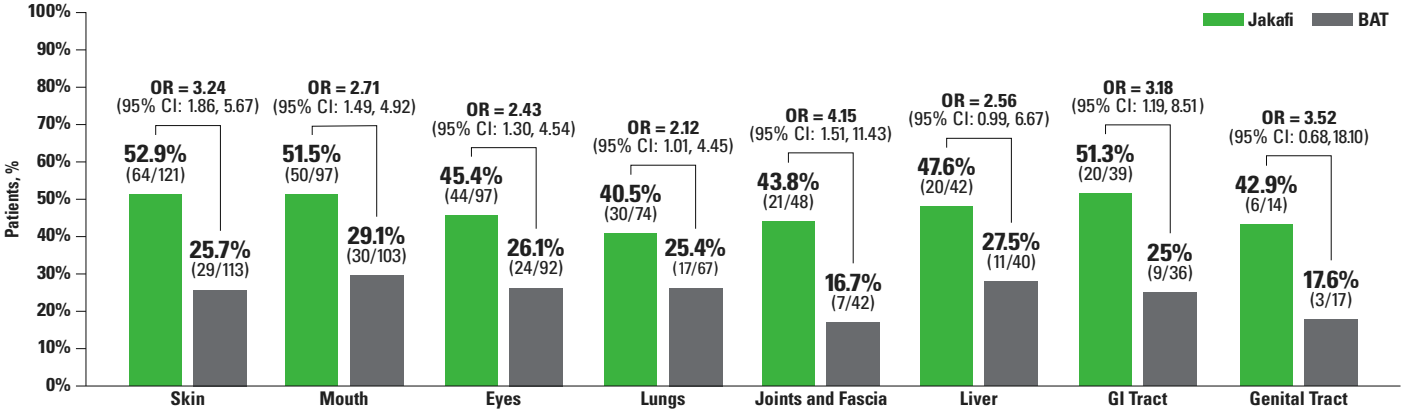


BAT, best available therapy; CR, complete response; cGVHD, chronic graft-versus-host disease; OR, odds ratio; PR, partial response.
[a]Moderate cGVHD was defined as ≥1 organ (not lung) with a score of 2, ≥3 organs with a score of 1 in each organ, or lung score of 1.[6]
[b]Severe cGVHD was defined as ≥1 organ with a score of 3 or lung score of 2 or 3.[6]

In addition, the impact of Jakafi is consistent across all organs, including the skin, mouth, and eyes, where earlier signs and symptoms are most common.[4,5] Response was also seen in more challenging organs to treat, such as the lungs.[5] (Figure 2)

Figure 2

REACH3: Subgroup Analysis of Overall Response Rates at Week 24 by Organ Involvement at Baseline[5,a]



BAT, best available therapy; cGVHD, chronic graft-versus-host disease; GI, gastrointestinal; OR, odds ratio.
[a]Patients with >1 affected organ were counted in each organ subgroup. Organ involvement was defined as organ score ≥1 based on the cGVHD staging criteria.[5]
*BAT was chosen by the investigator prior to randomization, options included: ibrutinib, extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, rituximab, everolimus, sirolimus, imatinib, infliximab, or pentostatin.[3]

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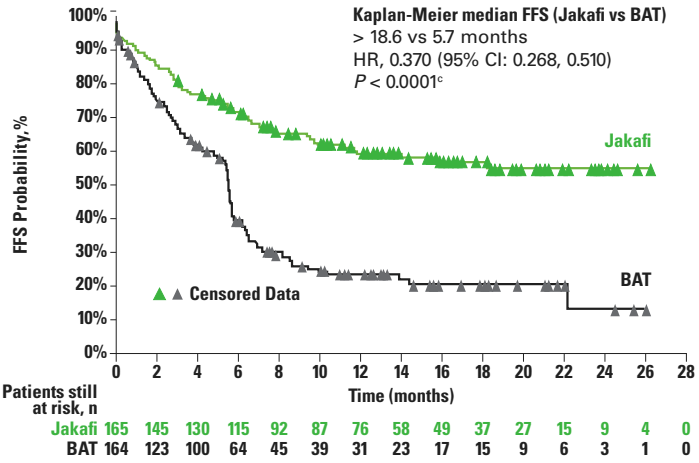
These data reflect my own experience and reinforce the importance of intervening at first signs of initial systemic treatment failure to achieve the higher response rate while the disease is still at its moderate severity.

Failure-free survival is another important measure of the long-term outcomes of treatment I value in my chronic GVHD patients. In REACH3, estimated probability of failure-free survival with Jakafi® (ruxolitinib) — defined as relapse, needing additional treatment for chronic GVHD, or death – was 74.9% (95% CI: 67.48, 80.85) at 6 months and 64% (95% CI: 55.78, 71.09) at 12 months, compared with 44.5% (95% CI: 36.46, 52.14) and 29.6% (95% CI: 22.34, 37.23) at respective timepoints with BAT.[4,6] Median failure-free survival with Jakafi was not reached.[5] (Figure 3)

Figure 3

REACH3 Key Secondary Endpoint: KM Analysis of Failure-Free Survival[4,6,a,b]



BAT, best available therapy; cGVHD, chronic graft-versus-host disease; FFS, failure-free survival; HR, hazard ratio; KM, Kaplan-Meier.

[a]Defined as the earliest time from date of randomization to relapse or recurrence of underlying disease or death due to underlying disease, non-relapse mortality, or addition or initiation of another systemic therapy for cGVHD.[4,6]

[b]37.2% of patients switched to Jakafi when permitted (after Week 24) and are included in the FFS assessment.

[c]Descriptive *P* value (ex-US only). Efficacy boundary crossed at the interim analysis (HR, 0.315; 95% CI: 0.205, 0.486; $P < 0.0001$). For US, the *P* value gives the result of the retested hypothesis at the primary analysis, following the overall hierarchical testing procedure.[6]

These data support my treatment approach where I start my patients on 10 mg BID to achieve a response. I evaluate blood parameters before and during treatment with Jakafi. Dose reductions should be considered based on platelet counts, absolute neutrophil counts or bilirubin elevations, or other adverse reactions as described in the Full Prescribing Information for Jakafi.[†] After achieving a desired response, I maintain them on the lowest tolerable dose over time to help them potentially achieve sustained benefits and help prevent flare-ups and potentially achieve my goal of failure-free survival.

[†]Doses may be modified based on safety and efficacy. Dose reductions may be used to manage side effects: 10 mg twice daily may be reduced to 5 mg twice daily; 5 mg twice daily may be reduced to 5 mg once daily. Patients who are unable to tolerate Jakafi at 5 mg once daily should have treatment interrupted until their clinical and/or laboratory parameters recover. Tapering may be considered after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids. Taper Jakafi by 1 dose level approximately every 8 weeks (10 mg BID to 5 mg BID to 5 mg QD). If GVHD signs or symptoms recur during or after the taper of Jakafi, consider retreatment.

Most Common Adverse Reactions With Jakafi vs BAT[3]

The most frequent (occurring in ≥10% patients) adverse reactions (all grades) (Jakafi vs BAT) are infections with pathogen not specified (45% vs 44%), viral infections (28% vs 23%), musculoskeletal pain (18% vs 13%), hypertension (16% vs 13%), pyrexia (16% vs 9%), cough (13% vs 8%), fatigue (13% vs 10%), hemorrhage (12% vs 15%), nausea (12% vs 13%), dyspnea (11% vs 8%), edema (10% vs 12%), and diarrhea (10% vs 13%). Selected hematological laboratory abnormalities (all grades) (Jakafi vs BAT) include anemia (82% vs 75%), thrombocytopenia (58% vs 54%), and neutropenia (27% vs 23%); selected chemical laboratory abnormalities (all grades) include hypercholesterolemia (88% vs 85%), increased gamma glutamyltransferase (81% vs 75%), elevated alanine aminotransferase (73% vs 71%), elevated aspartate aminotransferase (65% vs 54%), increased creatinine (47% vs 40%), elevated lipase (38% vs 30%), and elevated amylase (35% vs 25%).[3]

BAT, best available therapy

Summary

- My approach to managing patients with chronic GVHD is to intervene early to potentially control progression and prevent any irreversible damage
- I take a thorough history to uncover any early signs and symptoms and intervene with Jakafi at first signs of initial systemic treatment failure
- The Jakafi clinical data reflect my own clinical experience and reinforce the importance of early intervention, when the disease is moderate, regardless of organ involved to potentially achieve sustained benefits for the patient

References

1. Cooke KR, Luznik L, Sarantopoulos S, et al. The biology of chronic graft-versus-host disease: a task force report from the National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2017;23(2):211-234. doi:10.1016/j.bbmt.2016.09.023
2. Flowers MED, Martin PJ. How we treat chronic graft-versus-host disease. *Blood*. 2015;125(4):606-615.
3. Jakafi [package insert]. Wilmington, DE: Incyte Corporation.
4. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med*. 2021;385(3):228-238. doi:10.1056/NEJMoa2033122
5. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease [supplemental appendix]. *N Engl J Med*. 2021;385(3):228-238. doi:10.1056/NEJMoa2033122
6. Data on file. REACH3. Incyte Corporation. Wilmington, DE.

Scan the QR Code

to watch Karolina Faysman, MSN, AOCNP, share her clinical perspective around management of cGVHD.

For additional resources and educational content for advanced practice providers, visit hcp.jakafi.com.

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Indications and Usage

Jakafi® (ruxolitinib) is indicated for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

Important Safety Information

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Herpes zoster infection has been reported in patients receiving Jakafi. Advise patients about early signs and symptoms of herpes zoster and to seek early treatment. Herpes simplex virus reactivation and/or dissemination has been reported in patients receiving Jakafi. Monitor patients for the development of herpes simplex infections. If a patient develops evidence of dissemination of herpes simplex, consider interrupting treatment with Jakafi; patients should be promptly treated and monitored according to clinical guidelines
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers (NMSC) including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- Another JAK-inhibitor has increased the risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke (compared to those treated with tumor TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur
- Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with myelofibrosis (MF) and polycythemia vera (PV) treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately
- Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers
- In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >50%) were infections (pathogen not specified) and edema. In chronic graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >20%) were infections (pathogen not specified) and viral infections
- Avoid concomitant use with fluconazole doses greater than 200 mg. Dose modifications may be required when administering Jakafi with fluconazole doses of 200 mg or less, or with strong CYP3A4 inhibitors, or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for 2 weeks after the final dose

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