# ADVANCES IN LLM

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## GVHD Prophylaxis for Patients Undergoing Stem Cell Transplant

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**H&O** What is the classic backbone regimen used after allogeneic stem cell transplant (SCT)?

**PK** The traditional gold standard for graft-versus-host disease (GVHD) prophylaxis following allogeneic SCT is the combination of a calcineurin inhibitor—either tacrolimus or cyclosporine—and a short course of methotrexate that is typically given on days 1, 3, 6, and 11 after the stem cell infusion.

**H&O** How does this prophylaxis strategy differ across donor types?

**PK** The landscape of GVHD prophylaxis has evolved from a universal calcineurin inhibitor backbone to a highly stratified, evidence-based strategy. The most significant recent advancement is the broad adoption of post-transplant cyclophosphamide (PTCy).

Historically, PTCy was reserved exclusively for haploidentical transplants to manage the high degree of donor-recipient HLA mismatch. However, the landmark phase 3 BMT CTN 1703 trial transformed this approach by demonstrating that PTCy is effective across all donor types, including matched related and unrelated donors.[1]

In this trial, the experimental regimen—consisting of cyclophosphamide, tacrolimus, and mycophenolate mofetil (MMF)—proved superior to the traditional gold standard of tacrolimus and methotrexate. On the basis of these findings, many leading transplant centers have shifted their standard of care, replacing conventional, methotrexate-based regimens with PTCy-based prophylaxis for both matched related and unrelated donor transplants.

In the haploidentical and mismatched unrelated settings, the risk of alloreactivity is much higher. In adults, we rely almost exclusively on the PTCy protocol to deplete alloreactive T cells selectively. In pediatrics, however, we often use ex vivo T-cell depletion (specifically alpha/beta T- and B-cell depletion). By removing the "bad" T cells from the bag before infusion, we can often avoid post-transplant immunosuppression entirely, which is a significant advantage in children.

GVHD prophylaxis is uniquely tailored for cord blood transplants owing to the inherently prolonged engraftment kinetics of umbilical cord cells. Because methotrexate can further delay hematologic recovery and exacerbate the severe mucositis often seen in this setting, it is avoided by most transplant centers. Instead, the preferred standard for cord blood is a calcineurin inhibitor combined with MMF, which provides effective T-cell suppression without compromising engraftment.

**H&O** What role does antithymocyte globulin (ATG) play?

**PK** In the setting of matched unrelated donor transplants, ATG is frequently added to the calcineurin inhibitor and methotrexate backbone to achieve in vivo T-cell depletion. Although ATG significantly reduces the incidence of both acute and chronic GVHD—particularly more severe forms—its use is associated with delayed immune reconstitution, which increases the risk for viral reactivation and potentially compromises the graft-versus-leukemia effect.

**H&O** Does the intensity of the conditioning regimen affect the GVHD prophylaxis regimen that is used?

**PK** In the modern era, GVHD prophylaxis is driven primarily by donor type and organ function rather than by conditioning intensity alone. Because reduced-intensity conditioning or nonmyeloablative regimens are typically reserved for older or frailer patients, the choice of prophylaxis must be highly sensitive to their specific physiologic reserves. For instance, we generally avoid PTCy in patients with baseline cardiac dysfunction owing to the risk of cyclophosphamide-induced cardiotoxicity. Similarly, methotrexate is often withheld from patients with severe nutritional deficits or mucosal fragility. In these clinical scenarios, a combination of tacrolimus and MMF is used to minimize toxicities that could otherwise impair recovery or oral intake.

**H&O** Does the stem cell source—bone marrow vs peripheral blood—influence the choice or intensity of GVHD prophylaxis?

**PK** Peripheral blood stem cells contain a significantly higher percentage of T cells than bone marrow does. Consequently, the risk of acute and chronic GVHD is higher with peripheral blood stem cells than with bone marrow transplants. This higher risk often necessitates more intensive or prolonged prophylaxis, such as the addition of ATG or PTCy.

**H&O** Are the regimens that we have discussed aimed at preventing acute GVHD, chronic GVHD, or both?

**PK** The traditional backbone of a calcineurin inhibitor plus methotrexate was originally designed to prevent acute GVHD. However, it is now well established that severe acute GVHD is the primary risk factor for the subsequent development of chronic GVHD. The inflammatory environment created by early acute GVHD effectively "primes" the immune system for the fibrotic, multiorgan involvement characteristic of the chronic phase. By utilizing newer, more potent regimens that effectively suppress acute GVHD, we can interrupt this progression and significantly reduce the long-term incidence of chronic GVHD.

**H&O** What is the role of sirolimus in prophylaxis?

**PK** Sirolimus and other mammalian target of rapamycin (mTOR) inhibitors are versatile agents that can be utilized as monotherapy or in combination with a calcineurin inhibitor. The most frequent clinical application is the tacrolimus and sirolimus doublet, which many centers employ as an alternative to methotrexate-based regimens to avoid severe mucosal toxicity. Additionally, sirolimus can serve as a substitute for tacrolimus or cyclosporine in patients who cannot tolerate calcineurin inhibitors, particularly those at high risk for significant renal impairment.

**H&O** What is the role of abatacept, and in which patient population is this most relevant?

**PK** Abatacept (Orencia, Bristol Myers Squibb) is a first-in-class costimulation blocker that targets the CD80 and CD86 receptors on antigen-presenting cells. Its primary mechanism is inhibition of the "second signal" essential for T-cell activation and expansion. By interrupting this pathway, abatacept prevents the alloreactive T-cell response that leads to GVHD. It is currently approved by the US Food and Drug Administration (FDA) for GVHD prophylaxis in both adult and pediatric patients receiving transplants from unrelated donors. Abatacept is most clinically significant in the 7/8 HLA-mismatched unrelated donor setting, in which the incidence of severe acute GVHD is traditionally high. Unlike broader T-cell depleting strategies, the use of abatacept reduces the risk of severe acute GVHD without a significant increase in relapse or nonrelapse mortality.

**H&O** What is the role of ruxolitinib?

**PK** Ruxolitinib (Jakafi, Incyte) is a selective JAK1/2 inhibitor that has transformed the management of GVHD, serving as the standard of care for corticosteroid-refractory disease. For acute GVHD, the REACH1 and REACH2 trials established the superiority of ruxolitinib over best available therapies.[2,3] Similarly, the REACH3 phase 3 trial demonstrated that ruxolitinib significantly improves response rates and survival in chronic GVHD.[4]

Beyond treatment, JAK inhibitors are now being investigated for prophylaxis. The goal is to suppress the inflammatory cytokine storm that immediately follows transplant. For example, the JAK1 inhibitor itacitinib is being studied alongside PTCy in the haploidentical setting to reduce the incidence of severe GVHD and cytokine release syndrome.

Although highly effective in the corticosteroid-refractory and preventative settings, JAK inhibitors have not yet succeeded as upfront therapy. The GRAVITAS-301 trial showed that adding itacitinib to initial corticosteroids did not improve outcomes in comparison with corticosteroids alone.[5] Consequently, ruxolitinib remains primarily a second-line standard and a promising prophylactic agent.

**H&O** What other emerging agents are showing promise in GVHD prevention?

**PK** Several emerging agents are being investigated to refine GVHD prevention further, particularly through

organ-specific targeting. Vedolizumab (Entyvio, Takeda), a gut-selective integrin antagonist, is currently under study for its ability to block alloreactive T cells from migrating into the intestinal mucosa, thereby preventing GVHD within the gastrointestinal tract.

Another promising approach involves the use of oral budesonide, a locally acting corticosteroid characterized by a high rate of first-pass metabolism. Our published data demonstrate that incorporating oral budesonide into a PTCy backbone effectively reduces the incidence of acute gastrointestinal GVHD.[6] This strategy allows high local concentrations of drug in the gut while avoiding the significant systemic toxicities typically associated with corticosteroid use.

The experimental JAK1 inhibitor itacitinib is also being investigated for use in GVHD prophylaxis. A phase 1 study of patients undergoing haploidentical transplant, published in *Blood*, demonstrated that a combination of itacitinib and PTCy was exceptionally effective in preventing severe acute GVHD.[7]

## H&O When and how should calcineurin inhibitors be tapered, and what factors influence that decision?

**PK** The tapering of calcineurin inhibitors typically commences between days 60 and 90 for matched related donors and between days 100 and 180 for unrelated donors, provided no active GVHD is present. This process requires a highly individualized approach because several critical factors influence the likelihood of a successful withdrawal. According to data from Pidala and colleagues, specific donor and graft characteristics significantly increase the risk of taper failure. Patients receiving peripheral blood stem cells rather than bone marrow, those with mismatched unrelated donors, and those older than 50 years are at a substantially higher risk of experiencing GVHD flares during or after the reduction of immunosuppression.[8] These variables must be carefully weighed when the taper schedule for each patient is tailored.

Furthermore, we must remain vigilant for a decrease in donor chimerism or the emergence of measurable residual disease. In such high-risk clinical scenarios, we may choose to accelerate the taper to harness a more potent graft-versus-leukemia effect, although we do so with the understanding that accelerating the taper significantly increases the probability of triggering GVHD. Tapering, therefore, remains a delicate balance between achieving immune tolerance and maintaining adequate disease control.

## H&O What is the overall duration of GVHD prophylaxis regimens, and how is that determined?

**PK** The traditional goal for GVHD prophylaxis is 6 to 9 months. However, long-term data suggest a much more complex reality, in which only 20% of patients were alive and successfully off all immunosuppression 5 years after transplant.[8] This indicates that for the vast majority of patients, what begins as a short-term prophylaxis regimen often transitions into the long-term management of subclinical or overt chronic GVHD.

## H&O How do patient comorbidities affect the choice of prophylactic regimen?

**PK** The presence of pre-existing comorbidities is a critical factor when a GVHD prophylaxis strategy is selected. For example, we generally avoid high-dose PTCy in patients with a significant cardiac history because it can exacerbate underlying heart conditions.

In patients with baseline renal dysfunction, we often steer away from calcineurin inhibitors because of their nephrotoxicity, opting instead for sirolimus or MMF. We also need to consider that calcineurin inhibitors, sirolimus, and certain JAK inhibitors are metabolized by the liver; in patients with hepatic dysfunction, we must either avoid these agents or implement very strict monitoring to prevent further injury.

Finally, for patients at high risk for infection—especially those with a history of viral reactivation—we typically avoid agents that deplete T cells, such as ATG. These drugs can significantly prolong the time it takes for the immune system to recover, which only increases the risk of serious viral complications.

***Disclosures***

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## References


1. Bolaños-Meade J, Hamadani M, Wu J, et al; BMT CTN 1703 Investigators. Post-transplantation cyclophosphamide-based graft-versus-host disease prophylaxis. *N Engl J Med.* 2023;388(25):2338-2348.
2. Jagasia M, Perales MA, Schroeder MA, et al. Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial. *Blood.* 2020;135(20):1739-1749.
3. Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. *N Engl J Med.* 2020;382(19):1800-1810.
4. Zeiser R, Polverelli N, Ram R, et al; REACH3 Investigators. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med.* 2021;385(3):228-238.
5. Zeiser R, Socié G, Schroeder MA, et al. Efficacy and safety of itacitinib versus placebo in combination with corticosteroids for initial treatment of acute graft-versus-host disease (GRAVITAS-301): a randomised, multicentre, double-blind, phase 3 trial. *Lancet Haematol.* 2022;9(1):e14-e25.
6. Kongtim P, Chumnumsiriwath P, Vittayawacharin P, et al. Budesonide, added to PTCy-based regimen, for prevention of acute GI GVHD after allogeneic stem cell transplantation. *Am J Hematol.* 2025;100(3):383-392.
7. Abboud R, Schroeder MA, Rettig MP, et al. Itacitinib for prevention of graft-versus-host disease and cytokine release syndrome in haploidentical transplantation. *Blood.* 2025;145(13):1382-1394.
8. Pidala J, Martens M, Anasetti C, et al. Factors associated with successful discontinuation of immune suppression after allogeneic hematopoietic cell transplantation. *JAMA Oncol.* 2020;6(1):e192974.