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COMMENTARY

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Harnessing circadian timing to reduce aGVHD: A new paradigm in stem cell transplantation

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INTRODUCTION

Acute graft-versus-host disease (aGVHD) remains a formidable challenge in the field of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Despite advancements in prophylactic immunosuppression and donor selection strategies, aGVHD continues to limit post-transplant survival and quality of life.[1] Conventional approaches have primarily focused on inhibiting donor T-cell function through pharmacological or cellular means; however, the role of host-intrinsic circadian biology has received comparatively little attention.

The influence of circadian rhythms on immune function has been well documented. As early as the 1960s, innate immune responses were shown to be under circadian control, and a decade later, adaptive immune responses were also demonstrated to exhibit time-dependent variation. Contemporary studies have revealed that the biological clock regulates leukocyte trafficking between organs and dynamically modulates leukocyte counts in specific tissues throughout the day. In peripheral circulation, total leukocyte numbers peak during the rest phase in nocturnal animals (e.g., mice) and during the night in diurnal species (e.g., humans). Furthermore, in adaptive immunity, effector cell migration, activation, and cytokine production all display temporal dependence.[2]

In this context, our recent study published in *Cell*,[3] introduces a novel concept: the timing of stem cell infusion can significantly influence transplant outcomes through circadian regulation of host immunity. This commentary critically examines the study's key findings, mechanistic insights, and broader implications for transplantation immunology.

KEY FINDINGS: TIMING AS A THERAPEUTIC VARIABLE

A major strength of this study is the convergence of evidence from diverse preclinical models and multicenter clinical datasets, all pointing to the recipient's circadian rhythm as a key determinant of aGVHD risk and transplant outcomes. In the preclinical setting, both MHC-mismatched aGVHD and humanized xenogeneic GVHD murine models were employed to investigate the effect of infusion timing. Strikingly, mice infused during the biologically active phase exhibited significantly attenuated clinical and histopathological manifestations of aGVHD and prolonged survival compared to those transplanted during the rest phase. Importantly, experiments using *Per*1/2 knockout mice and animals with lesions of the suprachiasmatic nucleus confirmed that these effects are driven by the endogenous circadian clock rather than by external light cues. Reciprocal transplants between donors and recipients with mismatched circadian phases further demonstrated that it is the recipient's internal rhythm, not the donor's, that governs the outcome.

These findings were echoed in a retrospective clinical analysis encompassing five major transplant centers in China. Among hundreds of patients undergoing peripheral blood stem cell transplantation (PBSCT), those receiving infusions before 2:00 p.m. consistently experienced lower grades of aGVHD and improved survival, underscoring the translational relevance of the preclinical observations.

MECHANISTIC INSIGHTS: CIRCADIAN REGULATION OF INFLAMMATION

Beyond establishing the clinical and experimental correlation between infusion timing and aGVHD, the study probed the underlying biological mechanisms. Analysis of inflammatory mediators revealed that infusion timing intersects with the host's circadian-controlled immune microenvironment. Specifically, early-daytime infusions were associated with lower circulating levels of proinflammatory cytokines—most notably interleukin-1α (IL-1α)—compared with later-day infusions.

This temporally favorable immune milieu reduced early donor T-cell activation and proliferation, providing a mechanistic basis for the observed protection. Further supporting this conclusion, prophylactic administration of an anti-IL-1α monoclonal antibody in rest-phase–transplanted mice effectively recapitulated the protective effects of early infusion, confirming IL-1α as a key mediator (Figure 1).

Beyond IL-1α, circadian regulation encompasses multiple immune pathways. The biological clock coordinates leukocyte trafficking, oscillatory cytokine networks (e.g., IL-6, TNF-α), and antigen-presenting cell (APC) function. Hormonal and neural signals, including glucocorticoids and sympathetic tone, also affect how responsive T cells are to stimulation. Together, these mechanisms explain how infusion during a low-inflammation phase can reduce early donor T-cell activation and lower the risk of aGVHD.[2]

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

This work proposes a highly appealing, cost-neutral intervention: optimizing stem cell infusion timing within the existing clinical workflow. If validated in prospective trials, this approach could become a simple yet powerful tool to reduce aGVHD incidence, particularly in high-risk patient populations.

Nevertheless, several critical questions remain. First, the inherent limitations of retrospective analyses and the heterogeneity of patient cohorts cannot be overlooked. Potential confounders include comorbidities, concomitant medication exposures, and center-specific variations. Notably, differences across centers in the recognition of aGVHD, as well as in prophylaxis strategies and procedural workflows, may have influenced the results of our multicenter retrospective analysis. Incorporating center-level random effects, stratification, and harmonized protocols in future trials will be critical to strengthen causal inference. Second, it remains to be determined whether circadian modulation applies uniformly across different graft sources and preservation conditions, such as unrelated donor grafts or cryopreserved products. Notably, a recent study in unrelated fully matched PBSCT examined graft arrival time at the transplant center, rather than the actual infusion start time, in relation to GVHD risk.[4] This methodological difference may influence the accuracy of evaluating circadian effects. In China, unrelated donor grafts are often collected in different regions and transported over long distances, making it rarely feasible to achieve infusion before 2:00 p.m. Furthermore, transport mode and duration may substantially prolong the interval from collection to infusion, introducing additional variability. For these reasons, unrelated donor transplantation was not included in our cohort. To address these limitations and more accurately assess the role of infusion timing across different transplant types, we have initiated three prospective randomized controlled trials, two in PBSCT and one in unrelated cord blood transplantation (NCT06294678, NCT06294691, and NCT07047456).

Third, while our data identify 2:00 p.m. as a practical cutoff in PBSC transplantation, this threshold is, to some extent, operational rather than biological. Rather than adhering to a fixed clock time, the clinically relevant consideration is infusion during the host's low-inflammation phase, which may differ across individuals. In elderly recipients or those with circadian disruption, reliance on clock time alone may be misleading, and greater attention should be given to the immune environment immediately prior to infusion. The question remains whether even earlier infusions could yield greater benefit. In our unpublished retrospective analysis of cord blood transplantation cohorts, we found that even within the morning-to-noon window, the absolute infusion time remained an independent risk factor for severe aGVHD, underscoring the importance of performing stem cell infusion as early as possible during the day. This observation warrants validation in prospective studies.

Fourth, although IL-1α was identified as a pivotal cytokine, multiple other pro- and anti-inflammatory mediators displayed time-dependent variation. The complex interplay between these signaling pathways and the specific immune cell populations driving these changes requires further elucidation. Finally, assessing circadian patterns through monitoring of sleep, vital signs,

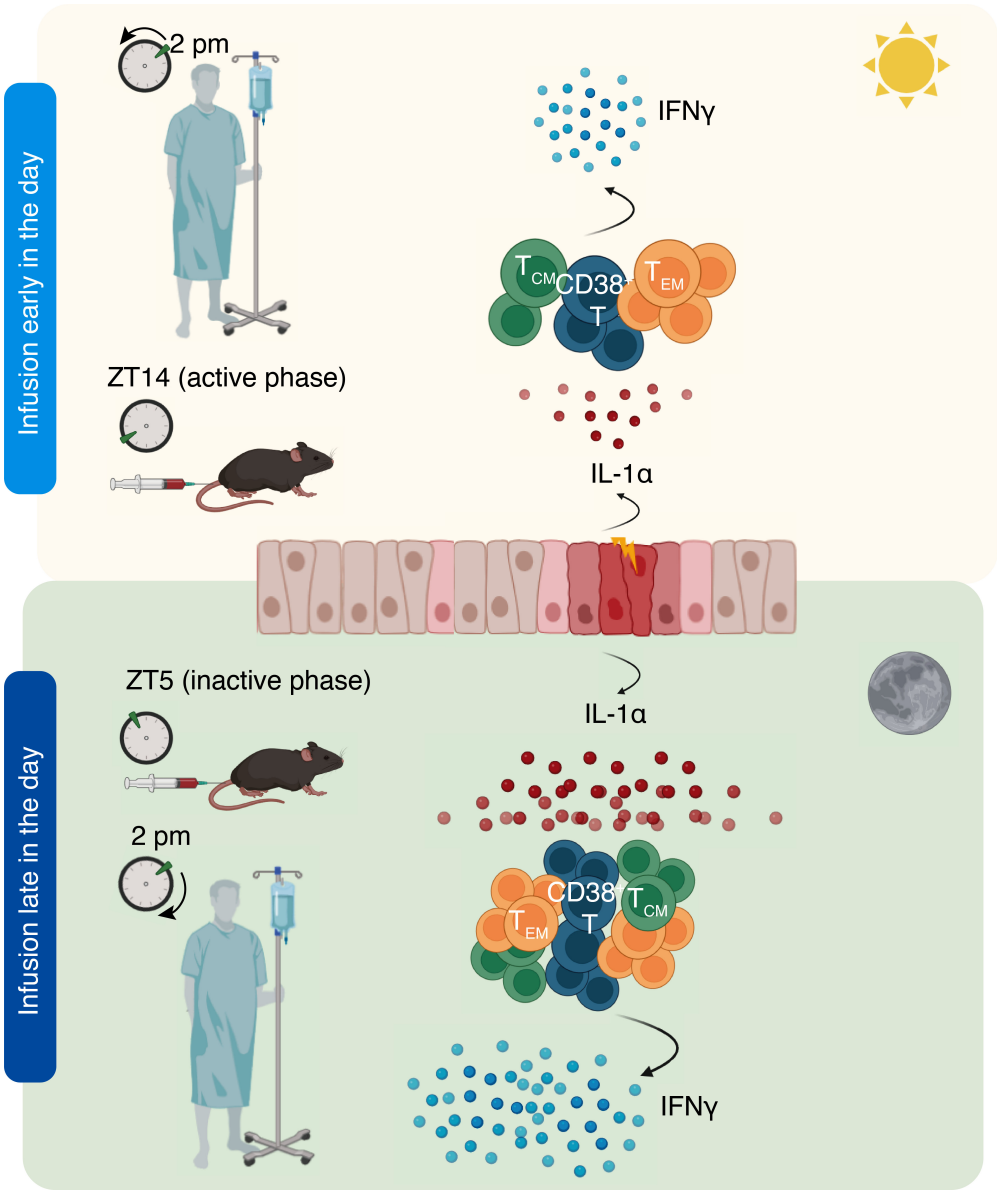

Figure 1. Clinical significance of stem cell infusion timing in reducing aGVHD after allo-HSCT Early daytime infusion coincides with lower levels of proinflammatory cytokines, especially IL-1α, creating a less inflammatory environment that suppresses donor T-cell activation and IFNγ release. These findings highlight infusion timing as a simple, cost-neutral, and clinically actionable strategy to improve transplant outcomes. In murine experiments, transplantation was performed at fixed ZT5 or ZT14, whereas in the human retrospective cohort infusion time was recorded as a continuous variable with a median of 2:00 p.m. For conceptual comparison, infusions before 2:00 p.m. are illustrated relative to murine ZT14, and those after 2:00 p.m. relative to ZT5.

and other physiological indicators, and evaluating their impact on therapeutic efficacy, should be explored in a broader range of clinical settings. Moreover, strategies for patients with disrupted circadian rhythms merit investigation, including whether physical or pharmacological interventions to restore circadian regularity could enhance transplant outcomes. Importantly, modern prophylaxis strategies (e.g., ruxolitinib, anti-CD25 antibodies, post-transplant cyclophosphamide, MSCs, anti-integrin antibodies) may reduce early donor T-cell activation and thereby diminish the marginal effect of timing.[5] Nevertheless, circadian optimization may retain value in higher-risk scenarios, such as mismatched or haploidentical transplantation, cord blood transplantation, or intensive conditioning regimens, where the baseline risk of aGVHD remains substantial. Moreover, individual circadian characteristics—including age, chronotype, or rhythm disruption due to illness—may further modulate the immune milieu at the time of infusion. These considerations suggest that timing strategies are unlikely to operate in isolation but could complement established prophylaxis and risk stratification to achieve maximal benefit.

Beyond transplantation, these findings may inform the optimization of other immune-based therapies, such as CAR-T cells, immune checkpoint blockade, and solid organ transplantation, through chronotherapeutic principles. Integrating wearable circadian biomarkers, time-based risk stratification, and personalized infusion schedules could redefine precision medicine in the transplant setting.

Taken together, our study suggests that the pre-infusion period represents a critical window for aGVHD intervention. The early activation state of donor T cells upon encountering the recipient immune milieu may be a decisive factor in the initiation of aGVHD. Thus, transient modulation of the recipient's proinflammatory environment immediately prior to stem cell infusion—by suppressing cytokines such as IL-1α—may provide an effective and practical strategy to prevent aGVHD. This concept not only highlights infusion timing as a clinically actionable variable but also points to novel opportunities for peri-transplant interventions targeting the earliest stages of alloreactive T-cell activation.

CONCLUSION

Our study marks a pivotal advance in recognizing time as an immunological modulator. By demonstrating that the host's circadian rhythm can shape alloreactive immune responses, this work reframes aGVHD prevention as not solely a matter of what is administered, but also when it is delivered.

While further validation in diverse clinical contexts is essential, this approach offers a pragmatic, evidence-based means to improve allo-HSCT outcomes. It invites transplant clinicians and immunologists to view the biological clock not as a passive background process, but as an active ally in optimizing therapeutic efficacy.

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AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.