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● ● ● TRANSPLANTATION

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Can Treg therapy prevent GVHD?

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In this issue of *Blood*, Brunstein and colleagues report the results of the first study to test the safety of human umbilical cord blood–derived regulatory T cells (Tregs), an approach designed to decrease graft-versus-host disease.¹ Transplanters, like Sisyphus of myth, have struggled mightily with trials of pharmacologic immunosuppressive drugs—we roll the rock up the mountain, only to see it roll back, leaving us where we began. This struggle has now led us to seek cellular therapies as a promising alternative.

Forty years ago, Gershon and Kondo made the seminal observation that a subpopulation of T cells could dampen the immune response, initiating a flurry of activity into the role of “suppressor T cells” in immunoregulation.² Further studies yielded conflicting data regarding their function, and in the 1980s interest in these cells collapsed like the recent mortgage bubble. A few tenacious investigators persisted, and in 1995 Sakaguchi and colleagues identified a subset of CD4⁺ T cells coexpressing CD25 (the IL-2 receptor α chain) as a thymus-derived population of peripheral T cells capable of inhibiting autoimmunity otherwise resulting from neonatal thymectomy.³ When murine T cells depleted of the CD4⁺CD25⁺ subpopulation were secondarily transferred, systemic autoimmunity developed, including a “graft-versus-host like wasting disease.”³ Eventually, this finding reignited the field of regulatory T-cell biology, with predictable enthusiasm from transplant immunologists.

Much has been learned from murine models, including that donor Tregs can reliably suppress graft-versus-host disease (GVHD),^{4,5} possibly sparing leukemia-specific immune responses,⁶ providing hope for more specific and less toxic immunosuppression than pharmacologic inhibitors. Other studies have addressed practical questions, including the cell doses required, and how to best expand ex vivo Treg derived from human peripheral blood and cord blood.⁷ Given the considerable preclinical promise of Tregs, the transplant community has anxiously awaited news of the first human clinical trials.

The present study tests the hypothesis that the addition of Tregs may improve allogeneic cord blood transplantation outcomes. A challenging aspect is to expand Tregs without also expanding conventional T cells. The authors’ prior studies suggested that cord blood–derived Tregs could be isolated with fewer selection steps than those from peripheral blood (due to the lack of CD25⁺ memory cells in antigen-naïve cords) and had excellent suppressor functions on a per-cell basis, even when HLA-mismatched to responder cells.⁷ In the current study, a third cord blood product would serve as the source of the Treg that would be expanded ex vivo and infused in the setting of an otherwise standard double-cord transplant.

This study treated 23 recipients in a “fast-track” dose-escalation design of Treg doses ranging from 1 to 30×10^5 Treg/kg recipient weight infused 1 day after the 2 unmanipulated cord blood products, with a subset of recipients also receiving second day +15 infusion.¹ The Tregs were isolated by CD25 magnetic bead isolation, and then expanded ex vivo for approximately 18 days using interleukin-2 and anti-CD3/anti-CD28 antibody-coated beads; this yielded a median expansion of > 200 -fold.

To the relief of those waiting in the wings with their own studies, no significant infusion toxicities were observed, despite the nontrivial risk that massively expanded T cells might have induced cytokine storm, or worse. There was no internal control group on this study, so outcomes were compared with a

group of historical controls (n = 108) from their institution. With respect to engraftment, normal kinetics of neutrophil and platelet recovery were observed. A key measure of the safety of infused Treg was the incidence of infections, a major cause of morbidity and mortality after cord blood transplantation⁸; while no functional studies of antigen-specific T-cell recovery were reported; no increases in cytomegalovirus or fungal infections were seen. Relapse rates were also similar to those in the historical control group. Given that this was primarily a phase I safety study, this trial was clearly a success; target cell doses were achieved in most subjects, and no appreciable toxicities were observed.

The most hoped for outcome of the study was a decreased incidence of GVHD, at least in individuals achieving the highest target Treg dose. The authors concluded there was a reduced incidence of grade II-IV acute GVHD in Treg recipients (43%) compared to the incidence in the historical control group (61%). It should be noted that another recent study from the same institution reported an incidence of 48% of grade II-IV acute GVHD in a group of 93 double-cord recipients with leukemia.⁹ Other recent reports have demonstrated even lower rates of acute GVHD. Thus, while the safety of the Treg infusions in this study was clear, their efficacy for reduction of GVHD was modest at best.

Some additional caveats are worth noting. First, even the highest dose of Tregs targeted amounted to a median ratio of Tregs:conventional cells of $\sim 1:5$, lower than that capable of reliably silencing GVHD in murine models,⁶ raising questions of whether an adequate dose of Tregs was administered. Higher Treg doses need to be explored. The study was designed to add Tregs to standard GVHD prophylaxis using cyclosporine. As noted by the authors, the calcineurin inhibitors may inhibit Treg function, which may have abrogated any potential beneficial effects of the Tregs on GVHD as well as adversely effecting immune reconstitution.¹⁰ Recent subjects received a sirolimus-based regimen, which would be predicted to be kinder to infused Tregs.¹⁰

Regulatory T cells may have adverse effects. Tregs are a major concern in cancer immunology where they have documented inhibitory activity on antitumor immunity. Just

as T-cell depletion has reduced the graft-versus-malignancy effects of allogeneic hematopoietic transplantation, infusion of Tregs may potentially increase the risk of recurrent malignancy; this can only be assessed in larger scale human trials. The “holy grail” in hematopoietic transplantation remains prevention of GVHD without impairing graft-versus-malignancy effects.

In the end, transplanters and translational immunologists should briefly rejoice. This careful study of infused Tregs has established their safety; modifications of this strategy may improve efficacy. Other investigators may now enter the fray with less trepidation.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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