Transplantation

Regulatory T cells fulfil their promise?

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Until now the common decision was to err on the side of infectious risk, by positively selecting CD34+ hematopoietic stem progenitor cells in the near-absence of T cells. There have been several attempts to mitigate the resulting 25% chance of infectious death, such as through infusing cytotoxic T-cell clones specific for the pathogens commonly responsible for post-HCT infections, such as cytomegalovirus and aspergillosis. As these treatments are technically challenging and do not provide a broad protection against infection, there is a strong need to develop a therapeutic strategy, which incorporates T-cell infusion while preventing GVHD. The concept of Treg infusion to prevent donor T-cell-driven GVHD has been around since the advent of suppressor T cells in the 1970s. The principle of Treg-mediated suppression of GVHD was demonstrated in mice, where the co-infusion of CD25+ Tregs and conventional T cells resulted in a reconstituted immune system without the advent of GVHD, while still preserving graft-versus-tumor activity.

In the forthcoming paper published in *Blood*, Di Ianni et al. adapted the mouse model of Treg cell therapy to haploidentical HCT patients. The trial was based on 28 high-risk adult patients suffering from advanced hematological malignancies. Patients received a stringent myeloablative conditioning regimen (Figure 1), followed by the infusion of freshly isolated donor CD25+ Tregs. Following this pre-conditioning, patients were transplanted with CD34+ hematopoietic stem cells, to reconstitute the bone marrow, and conventional T cells to reconstitute the immune system. As demonstrated previously with conventional T-cell infusion, immune reconstitution was fast, with CD4 and CD8 donor T-cell counts reaching the healthy range within 2–3 months and pathogen-specific clones expanding to counter infection. Most remarkably, of the 28 patients only 2 developed acute GVHD (≥ grade II) and none developed chronic GVHD, despite no immunosuppression being used. It is notable that this effect of Treg cell therapy in preventing GVHD is

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**Figure 1** Treg cell therapy schedule of the Di Ianni et al. study. Patients were conditioned through a regimen of 8 Gy total body irradiation, 200 mg m$^{-2}$ fludarabine total dose, 8 mg kg$^{-1}$ thiotepa total dose, and 70 mg kg$^{-1}$ cyclophosphamide total dose. On day −4, patients were infused with fresh Tregs isolated through leukapheresis ($2 \times 10^{6}$ Tregs kg$^{-1}$). On day 0, patients were infused with CD34$^+$ stem cells (mean dose: $9 \times 10^6$ cells kg$^{-1}$) and conventional T cells (0.5 to 4 $\times 10^6$ cells kg$^{-1}$).
much stronger than that observed in previous clinical trials utilizing ex vivo expanded Tregs, suggesting that critical functions or specificities are lost during the expansion process. While overall mortality from infection in the Di Ianni study was still high, the ability of Tregs to prevent GVHD after conventional T-cell infusion is very promising for future therapeutics.

The implications of this study for haplo-identical HCT are clear—for clinicians dealing with GVHD, Treg-cell therapy is a viable option. By manipulating the transplant schedule to involve Tregs and conventional T-cell transfer, Di Ianni et al. managed to stabilize the immunological balance toward both better control of tolerance (low GVHD) and prompt immune reconstitution. More broadly, however, this study shows that the use of Tregs in a clinical setting is not just a pipe dream, and that the fantastical proposals for the manipulation of Tregs in everything from autoimmunity to cancer may just end up being feasible.