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Transplantation

Regulatory T cells fulfil their promise?

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In the 15 years since the discovery of $CD25^+$ regulatory T cells (Tregs),[1] the potential for these cells to be exploited in the clinic has been much touted, especially since the explosion of research in the post-Foxp3 era. Hypothetical treatments have been proposed to boost Tregs in order to promote tolerance in the autoimmune or transplantation contexts, and to deplete Tregs in order to promote immunity against cancers or persistent infections. Whether Tregs would live up to the expectation has remained an open question, with mixed results in preliminary trials. A forthcoming paper by Di Ianni *et al.*[2] suggests that Tregs are indeed fulfilling expectations by making the transition from bench to bedside.

The study of Di Ianni *et al.*[2] used the important clinical context of haploidentical hematopoietic cell transplantation (HCT). HCT is a potentially curative option for many patients with hematological malignancies.[3] The ideal donor for HCT is a human leukocyte antigen-identical donor, but often only a donor sharing one human leukocyte antigen-haplotype is available, resulting in haploidentical HCT. Haploidentical HCT is a classic example of a clinical situation, in which the delicate balance between immunity and tolerance has yet to be reached. If T cells are included in the donor graft, graft-versus-host disease (GVHD) results, a life-threatening complication consisting of the destruction of recipient organs by donor T cells. By contrast, if T cells are depleted prior to transplantation, GVHD is avoided, but the risks of severe infections and tumor relapse are dramatically increased because of poor immune reconstitution.[4]

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.[5] 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.[6]

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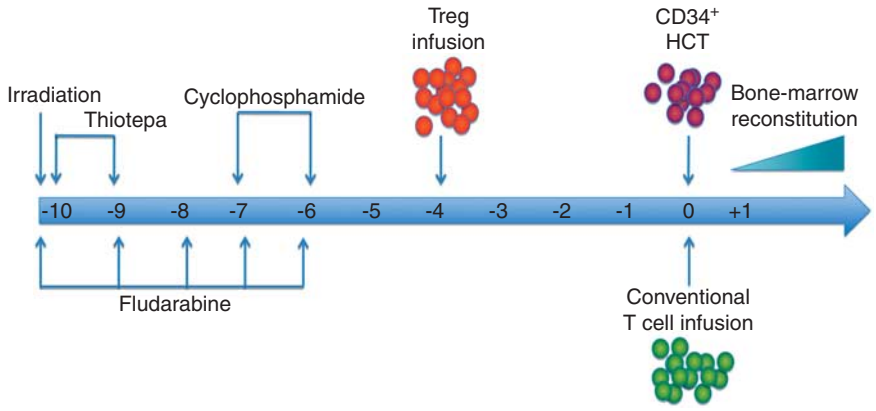

Figure 1 Treg cell therapy schedule of the Di Ianni *et al.*[2] study. Patients were conditioned through a regimen of 8 Gy total body irradiation, 200 mg m^{-2} fludarabine total dose, 8 mg kg^{-1} thiotepa total dose, and 70 mg kg^{-1} cyclophosphamide total dose. On day −4, patients were infused with fresh Tregs isolated through leukapheresis (2×10^6 Tregs kg^{-1}). On day 0, patients were infused with CD34$^+$ stem cells (mean dose: 9×10^6 cells kg^{-1}) and conventional T cells (0.5 to 4×10^6 cells kg^{-1}).

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,[7,8] while still preserving graft-versus-tumor activity.[9]

In the forthcoming paper published in *Blood*, Di Ianni *et al.*[2] 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.[2] 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 ($\geqslant$ grade II) and none developed chronic GVHD, despite no immunosuppression being used.[2] It is notable that this effect of Treg cell therapy in preventing GVHD is much stronger than that observed in previous clinical trials utilizing *ex vivo* expanded Tregs,[10] 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 haploidentical 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.*[2] 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.

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