# Organ Transplant Tolerance for Children; in Sight for Some

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Advances in tolerance protocols in adult organ transplantation have led to a number of patients coming off immunosuppression following transplantation. This success in transplant tolerance has been achieved using both mixed and full chimerism approaches at a number of centers in the US. Internationally, there are also ongoing studies in kidney transplantation using tolerogenic cell therapy that also aim to reduce or remove immunosuppression. This has suggested that "a kidney for life" is possible. Pediatric patients would be the main beneficiaries of such an outcome. Further, in liver transplantation, highly selected patients have been identified who have been able to come off immunosuppression.

We describe the current successes of these tolerance protocols and a discussion of the burden that such protocols would have for children, including an outline of selected pediatric groups where the barriers for enrollment in such protocols would be less and may be justified. In particular, patients with renal failure who may need a bone marrow transplant, patients with renal failure where a bone marrow transplant may benefit systemic disease, or a condition where the treatment of malignancy or bone marrow failure has already caused renal failure.

Solid organ transplantation in children is limited by long-term graft failure and the side-effects of immunosuppression, including cardiovascular disease and cancer. Kidney transplants are the most common solid organ transplant in children and have a limited expectancy of around 16-20 years with a living related graft. Improvements in graft survival over the last 40 years have occurred in the first 5 years after transplant, but there is a similar rate of graft loss after this.[1] Liver transplantation in children, although technically more difficult, often have better survival with the need for less immunosuppression; other organs such as hearts, lungs, and small bowel require strong immunosuppression to prevent rejection.

Transplant tolerance, where the patient's immune system is rendered tolerant to the graft, has been a major goal of transplantation. Despite great success in animal models, this has had very little success in human kidney transplants. This is in marked contrast to liver transplantation, where historically George Mazariegos began studies on weaning of immunosuppression in liver transplants, and where, under close supervision, a proportion of patients with a stable liver transplant for a number of years have been able to withdraw immunosuppression.[2,3] The major methods to achieve tolerance have been to alter immune recognition at the time of transplantation, such as co-stimulatory blockade, or to using bone marrow transplantation (BMT) to achieve either mixed or full hematopoietic chimerism to achieve tolerance, or to infuse a regulatory cell subset to induce tolerance. Full and mixed chimerism approaches have achieved clinical tolerance, where co-stimulatory blockade has failed, possibly reflecting the greater immune barrier in humans. Regulatory cell therapy, although of great interest, has only recently begun human trials in kidney transplants in the ONE Study and has also been proposed for use in combination with immune withdrawal in liver transplant recipients.

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| BMT | Bone marrow transplantation |

## Success in Adult Tolerance Programs

In adult transplantation, the clinical achievement of transplant tolerance has changed significantly, particularly in the last 5 years, where there has been improving results in 4 clinical programs of kidney transplantation in adults achieving transplant tolerance. These programs have included adults who had previously received kidney transplants as children.[4-7]

The first successful study is a trial from Massachusetts General Hospital, running for over 15 years, which has reported on 10 patients who received their mixed chimerism protocol, using a mixture of thymic irradiation, cyclophosphamide, T cell ablation, donor bone marrow peritransplant, and T cell infusions that achieved temporary mixed chimerism but long-term tolerance in over one-half of the patients treated with significantly less comorbidities than recipients of renal transplant receiving standard immunosuppression.[8] Issues with disease recurrence and antibody-mediated rejection have led to modification of the original Immune Tolerance Network protocol including the addition of B cell depleting antibodies with this study ongoing.

The Stanford group has successfully used total body irradiation and post-transplant anti-thymocyte globulin and donor hematopoietic cells enriched for CD34+ stem cells in a small number of patients with HLA matched kidney transplants that develop stable mixed or full chimerism and can come off immunosuppression, and has some limited experience with HLA mismatched transplants using the same

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protocol but where loss of chimerism has led to increased cell dosing.[6]

Northwestern University, Chicago, has used a fludarabine and irradiation myeloablative pre-transplant regime with donor bone marrow at the time of organ transplantation, and post-transplant cyclophosphamide, and "facilitator" cells following organ transplant. Patients are HLA mismatched; 12 of 19 patients have achieved full chimerism and are off immunosuppression at 12 months post-transplant. No patient has experienced graft vs host disease.[4]

John Hopkins, Baltimore, is conducting an Immune Tolerance Network trial of kidney transplantation in mismatched patients using high dose post-bone marrow transplant cyclophosphamide that has achieved full chimerism in a number of patients but where graft vs host still occurs, though at a lower rate.[7] These current studies in kidney transplantation are outlined in the Figure and Table.

## Regulatory Cell Therapy

Currently, there are a number of centers in Europe and the US treating patients with kidney transplants receiving standard immunosuppression, not including anti-CD25 antibodies, with recipient regulatory cell infusions post-transplant as part of the ONE Study.[9,10] These include Tregs, a subset of CD4 T cells that induces tolerance, Tr1 cells, a subset of CD4 T cells that secretes interleukin-10, Mregs, a subset of macrophages that have regulatory properties, and regulatory dendritic cells, a subset of dendritic cells that promote tolerance. Although no long-term tolerant patients have been reported, these studies are also aimed at immunosuppression withdrawal.

## Other Organs

Although current tolerance protocols are occurring in kidney transplants, success may lead to use in other organs such as liver, lungs, heart, and islets using either chimerism strategies or, in the case of liver transplants, Treg infusions combined with withdrawal of immunosuppression.

## International Review

The success of patients in these protocols has suggested that it is possible to have a "transplant for life" and that the greatest potential beneficiaries of this would be pediatric patients. A recent conference organized by the Transplantation Society made a number of recommendations about progressing tolerance protocols into the clinic. These included recommendation 4; that children 12 and older should be included in transplant tolerance protocols proven to be safe and effective in adults.[11] The adult tolerance studies currently underway have recently been reviewed in detail.[12]

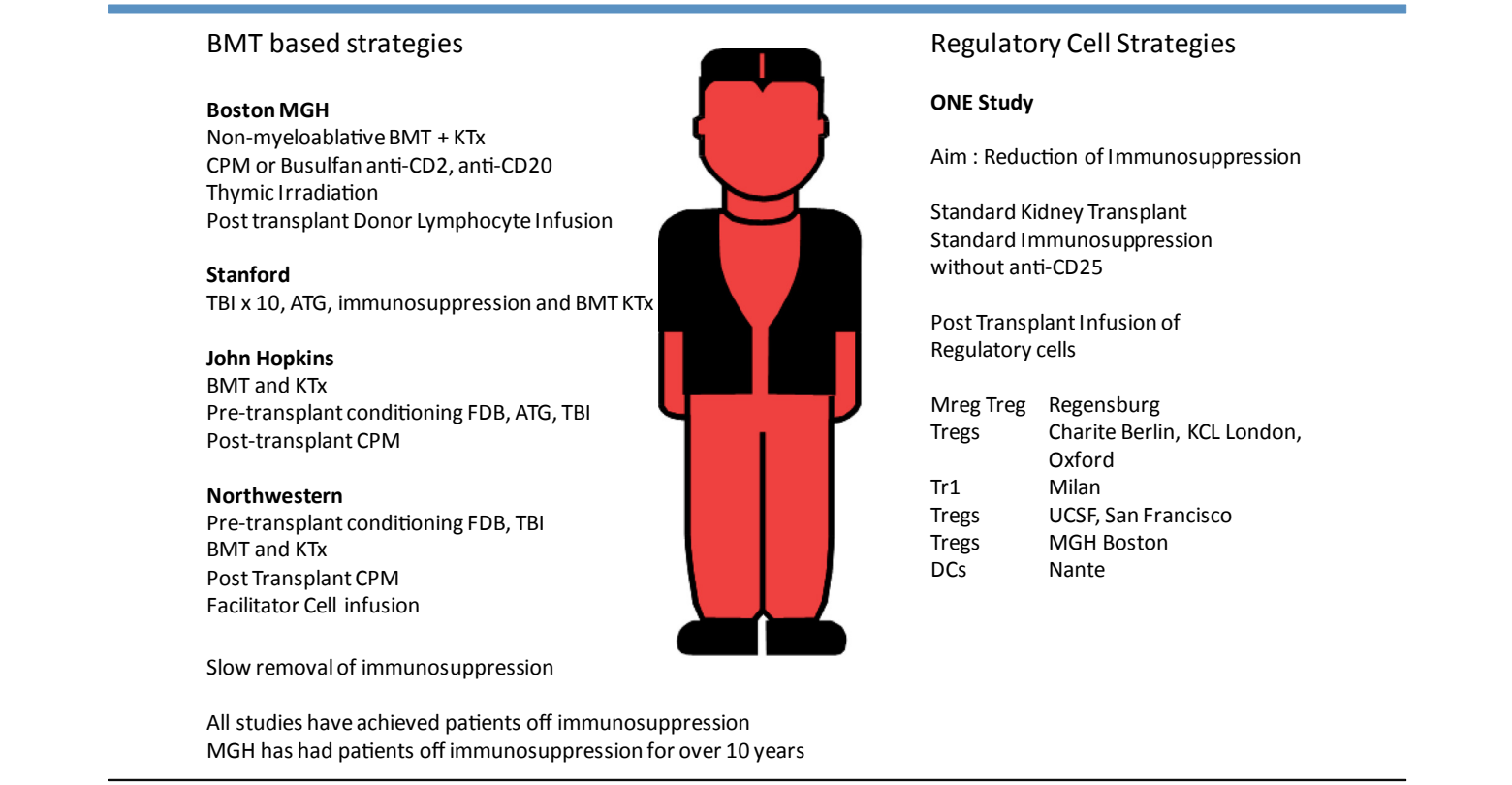


**Figure.** Two major groups of tolerance studies with studies on the *left* of BMT aimed at chimerism and, on the *right*, regulatory cell therapies. *ATG*, anti-thymocyte globulin; *CPM*, cyclophosphamide; *FDB*, fludarabine; *KTx*, kidney transplant; *MGH*, Massachusetts General Hospital; *TBI*, total body irradiation.