Kidney transplantation is the best treatment for patients with kidney failure, but improvements in long-term graft and patient survival have plateaued during the last few decades. Achieving the right balance between sufficient immunosuppression and risk for developing drug-related side effects such as infection, cancer, and cardiovascular diseases is difficult. Building on an increasing understanding of immunoregulatory cells and the revolution in cell-based therapies for cancer treatment, the time has come to test cell-based adoptive immunotherapy in transplant recipients to improve outcomes. In a recent issue of The Lancet, Sawitzki et al published initial findings of The ONE Study, a multicentric international phase 1/2A study that included 7 investigator-led single-arm trials to test the safety and efficacy of 6 different cell-based therapies in kidney transplantation.

This study compared the prevalence of biopsy-confirmed acute rejection (primary outcome) between a reference group trial (RGT) and a cellular therapy group (CTG) trial (composite of 6 independent studies) in nonsensitized adult living kidney transplant recipients. This trial included patients from 8 transplantation centers in Europe and the United States. The RGT was completed before any of the CTG trial enrollment started and is used as a comparison. In the RGT, all patients were treated with an identical immunosuppressive regimen consisting of basiliximab induction and maintenance with a triple immunosuppressive regimen of prednisolone tapered over 15 weeks, tacrolimus, and mycophenolate mofetil (Fig 1). The CTG trial was a composite trial of 6 different cell therapy products, each produced and administered in a different center (except for 1 cell product given at both Oxford and London). All patients were treated with the same immunosuppressive protocol, differing from the RGT only by replacement of basiliximab with the locally produced cell therapy product. Local investigators also had the option to taper and potentially discontinue mycophenolate mofetil therapy starting 9 months post-transplantation, leaving the patient on tacrolimus monotherapy (Fig 1). The different cell therapy products included 4 regulatory T cell (Treg)-based products (2 polyclonal and 2 donor-antigen reactive) and 2 monocyte-derived products (tolerogenic dendritic cells and regulatory macrophages). These cell types dampen immune responses in vitro, in animal models, and in studies of humans. All Treg preparations contained populations with different specificities (ie, nonclonal). Those generated in the United-States (termed donor-reactive) were expanded in response to donor antigens, whereas those produced in Europe (termed polyclonal) were expanded by nonspecific T-cell receptor stimulation and costimulation. All cell-based therapies were administered in an autologous manner (cells from the recipient) except for regulatory macrophages, which were allogenic (donor derived).


What Does This Important Study Show?

As a phase 1/2A trial, The ONE Study fulfilled its main purpose demonstrating the safety and feasibility of regulatory cell–based therapy in a kidney transplant population. After a median follow-up of 60 months, there were no differences in the primary outcome of biopsy-confirmed acute rejection (12% in the RGT vs 16% in the combined CTG trial) despite a lower immunosuppressive regimen in the latter. In the CTG trial, 17 of 38 (45%) were converted to tacrolimus monotherapy, which was successful in all except 2 cases (1 biopsy-confirmed acute rejection and 1 recurrent immunoglobulin A nephropathy).

Interestingly, adverse events related to infection were nearly 6 times higher in the RGT compared with the CTG trial. The difference started as early as the first weeks after transplantation and was stable over time (even before mycophenolate mofetil tapering), suggesting protection from the cell-based therapy and/or a deleterious effect from basiliximab. The main difference was in the number of viral infections, including cytomegalovirus, herpes virus, and polyomavirus. Strikingly, there were zero cases of cytomegalovirus infection reported in the cell-based therapy cohort compared with approximately 30 per 100 patient study-years with the RGT despite a higher percentage of high-risk cytomegalovirus-seropositive donor to seronegative recipient transplantations and equivalent antiviral prophylaxis.

A secondary outcome of these studies was detailed immunomonitoring. They showed major alterations in absolute and relative blood immune cell composition in patients participating in the reference group compared with age- and sex-matched healthy controls, in line with the current literature on the impact of uremia and dialysis on the immune system. Furthermore, and only in the CTG trial, patients had a healthy control-like restoration of
the immune system toward a more normal composition. Treg stability is a major potential safety issue, especially for donor-specific Tregs, because those cells would be perfectly fit to attack the graft if they converted to conventional T cells. However, the study showed that at 60 weeks there was no loss of Treg-specific demethylated region demethylation in the cell-therapy group, suggesting Treg stability.

The strengths of this study include the fact that this is the only cell-therapy trial in transplantation that used a reference group to compare outcomes, immunomonitoring, or adverse events. This uniquely designed study involved 8 centers from 5 different countries on 2 continents with their associated regulatory agencies, which represents in itself a real tour de force. The authors were able to demonstrate feasibility and safety using adoptive immunotherapies in kidney transplantation.

As for the weaknesses, we need to acknowledge that as a phase 1/2A trial, these studies were not designed to formally assess the efficacy of any specific cell therapy. Patients were not randomly assigned and physicians were not blinded to the group protocol. The number of treated patients in each trial was low, which prevents a comprehensive comparative analysis between all trials. Furthermore, the conclusions of the study are limited because in the CTG trial, the authors combined results of different trials, each one being different in terms of number of patients recruited and treatments.

Of note, from 782 patients assessed for eligibility, only 130 (17%) were enrolled and 104 were treated and included in the analysis, showing the complexity of such trials. In the CTG trial in particular, only 38 of the 60 enrolled patients were ultimately included. Of the excluded patients, 14 were excluded because the therapy could not be prepared on account of cell manufacturing failures. Five patients were also excluded because of acute rejection before the planned cell infusion. This is particularly important to consider if we want to move forward with cell therapy in the setting of deceased donor transplantation in which the delay between transplantation and cell infusion could be increased or would require a substantially different protocol. In addition, the short follow-up (60 weeks) precludes assessment of truly long-term graft function and chronic or antibody-mediated rejection. However, it is expected that analyses of each trial will be reported after longer follow-up. In addition, because most participants were recruited in European centers, patients of African descent were likely under- or unrepresented in the trial relative to their proportion among transplant recipients in the United States. Finally, both groups had an over-representation of male participants (73% in the RGT and 71% in the CTG trial), which could limit generalization of data to female transplant recipients.

How Does This Study Compare With Prior Studies?
Many cell-therapy trials to improve immunoregulation are ongoing, not only in transplantation but also to treat or prevent graft-versus-host disease and autoimmune diseases. However, very few of the studies in transplantation are published. Hutchinson et al first published preliminary work using regulatory macrophages in recipients of kidneys from living donors. This work paved the way to the trial that was part of The ONE Study. Mathew et al from Northwestern showed that Treg-adoptive immunotherapy is safe in patients receiving transplants with kidneys from living donors in a phase 1 dose escalation study. The group from San Francisco treated 3 patients with inflammation on their 6-month surveillance biopsies with Tregs.
They were able to demonstrate that Tregs persist in a range comparable to that of patients with type 1 diabetes not receiving immunosuppressive drugs. Finally, in a study in which T-cell–based therapy was injected into 10 living donor liver transplant recipients, Todo et al found that they were able to stop immunosuppressive drugs at 18 months in 7 of 10 patients. However, The ONE Study is the first multicentric international trial and the only one with a reference group, allowing for a better outcome comparison.

**What Are the Implications for Nephrologists?**

This is thus an exciting study that opens the way for the use of adoptive cell products as adjunctive immunotherapy in kidney transplant recipients. Notwithstanding the relative immunosuppression secondary to uremia and inflammation in patients with kidney failure, the data showed that they could culture and expand functional immune cells for autologous adoptive cell therapy. The administration of immunomodulatory cells could be used not only in transplantation but also to treat autoimmune disease.

Although practical, organizational, and technical aspects of cell-based therapy are complex and will need to rely on changes in infrastructure and monitoring, we can build on the advances made to treat patients with cancer. Many questions still need to be answered—how much, when, to whom, and which immunosuppressive protocol—but first and foremost, which cells. In addition to the type of regulatory cells and their source (blood, thymus, bone marrow, etc), cells can be genetically modified to improve specificity (using transgenic T-cell receptors or chimeric antigen receptors), homing (to the graft and lymph nodes), stability, and function. 11

Nephrologists will need to get familiar with cell therapy to limit clinical skepticism and fear that may be a barrier to use. This study is only the first step in a long walk through a wider implementation of cell-based immunomodulation in nephrology and transplantation.

**References**

10. Todo S, Yamashita K, Goto R, et al. A pilot study of operational immunosuppression secondary to uremia and inflammation in kidney transplant recipients. Notwithstanding the relative immunosuppression secondary to uremia and inflammation in patients with kidney failure, the data showed that they could culture and expand functional immune cells for autologous adoptive cell therapy. The administration of immunomodulatory cells could be used not only in transplantation but also to treat autoimmune disease.