Kidney transplantation: a safe step forward for regulatory immune cell therapy

On the basis of promising animal studies and following the translational path of immune cell therapy in oncology, the field of organ transplantation has begun preliminary investigations of infusing regulatory immune cells into graft recipients. These early trials aim to reduce patients’ immunosuppressive drug burden and promote drug-free transplant tolerance. The ONE Study was established in 2011 as a multicentre collaborative effort (centres in France, Germany, Italy, the UK, and the USA) to compare the feasibility, safety, and efficacy of regulatory cell-based medicinal products (CBMPs) when combined with reduced immunosuppressive treatment in low-risk, living-donor kidney recipients. In The Lancet, Birgit Sawitzki and colleagues relay an important general message of safety and similar rejection rates in the ONE Study when CBMPs were assessed. This finding was observed together with overall lower amounts of immunosuppressive therapy over a 60-week follow-up period compared with a reference group trial given standard-of-care immunosuppression. In addition to the reference group trial (n=66, 89% white, 73% men, median age 47 years), six small, single-armed, non-randomised phase 1/2A trials (total n=38, 95% white, 71% men, median age 45 years) were done. In each, a
single infusion of one of six CBMPs containing regulatory T cells (Tregs), dendritic cells, or macrophages was administered. The primary endpoint of biopsy-confirmed acute rejection within 60 weeks after transplantation was 16% in the cell therapy group trials and 12% in the reference group trial. The incidence of patients with donor-specific antibody at 60 weeks was 15% in the cell therapy group trials and 14% in the reference group trial, while increases in glomerular filtration rate over the study period were almost identical. Monitoring of host immune cells suggested a lower inflammatory state with fewer infections in the cell therapy group trials.

Several important considerations arise from the report. Each of the six participating centres gave a single infusion of one distinct cell type, with varying doses between types, either before or after transplantation, together with uniform triple drug immunosuppression (ie, tapered steroids, mycophenolate mofetil, and tacrolimus). Importantly, patients in the reference group trial also received basiliximab induction, which was excluded from the trial group (due to concerns that interleukin-2 antagonism might inhibit regulatory cell function), and lower doses of mycophenolate mofetil from week 2. Thus, the reference group trial was not a true control group. The lower incidence of infections seen in the cell therapy group trials might simply reflect lower general immunosuppression. An additional limitation is that the short follow-up did not allow assessment of clinical endpoints, including drug-associated effects and antibody-mediated rejection, which occur beyond 1 year.

In their analysis, the authors pooled data from each small trial of six distinct CBMPs (host or donor-derived, given before or after transplantation). Therefore, this study does not inform us as to which regulatory cell therapy regimen could be most worth pursuing. There is, however, a reassurance that analyses of each cell trial will be reported after longer follow-up to allow comparison between cell types.

The study illuminates the many formidable challenges facing the development of regulatory cell therapy. Practical and technological aspects of so-called living drug (and in the case of Tregs, dividing drug) treatment in transplantation are difficult to standardise and include the generation of good manufacturing practice cell products from patients with end-stage organ disease or those on immunosuppression. These cells might behave differently from those of healthy individuals. The complexities of cell therapy, including its reproducibility, are daunting to investigators, sceptical clinicians, and industry alike. Investigators and clinicians might see the approach as unproven, cumbersome, and not easily applicable. The cell products used in the ONE Study were manufactured on site in academic centres, after many years of dedicated, nuanced development by committed researchers. Numerous manufacturing failures (reported in this study to be 25%) highlight the need for manufacturing refinements and protocolisation. Eventual commercialisation, should it occur, will need to address the issues of unavoidable heterogeneity in cell populations and scalability. Protocol application could pose challenges since the practicality of timing of cell infusion is variable between centres and patients. The other myriad of immunological, medical, and surgical elements unique to each transplant patient bring forth the difficulty in standardising a cell therapy regimen outside of a highly selected group. Generating sufficient cells to meet target doses, ensuring that cells remain stable after infusion without loss of function, or become effectors, especially under inflammatory conditions, and that they mediate a durable effect, might be difficult to guarantee.

Where do studies of regulatory immune cell therapy go from here? Many key questions need answers, including whether the different cell products migrate to the desired sites (the graft or lymphoid tissue) and which are the most appropriate drug regimens to preserve or enhance their function. There are reasons for optimism. An encouraging uncontrolled trial from 2016 in Japan showed early,
complete withdrawal of immunosuppression and clinical tolerance in seven of ten liver recipients given post-transplant cyclophosphamide, followed by autologous, donor-reactive Tregs. As a result of the ONE Study, a randomised trial of polyclonal Tregs in kidney transplantation (the TWO Study) has been initiated in the UK, while US centres are pursuing renal and liver transplant trials with Tregs or regulatory dendritic cell products. In the laboratory, outpacing clinical testing, donor-specific (chimeric antigen receptor) Tregs are being assessed, while advanced engineering techniques (eg, CRISPR-based gene editing) are being used to enhance Treg specificity, stability, function, and delivery. Use of bone marrow or pluripotent stem cells (rather than rare peripheral blood cells) to generate regulatory cell products could pave a way to future trials. Alternative strategies to augment regulatory immune cell function by in-vivo targeting are also under consideration. It will be important to accompany emerging cell therapy trials with blood and intragraft analyses of mechanisms that might underlie the development of tolerance.

The ONE Study report conveys an important message of the safety of regulatory immune cell therapy in a select, low-risk group of transplant patients. The future promises longer follow-up reports of distinct cell types that could guide clinically pragmatic moves toward reduced immunosuppression and, eventually, tolerance.

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