Now or never? The case for cell-based immunosuppression in kidney transplantation

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By exploiting mechanisms of immunological regulation against donor alloantigen, it may be possible to reduce the dependence of kidney transplant recipients upon calcineurin inhibitor-based maintenance immunosuppression. One means to strengthen regulatory responses is treating recipients with preparations of regulatory cells obtained by *ex vivo* manipulation. This strategy, which is a well-established experimental method, has been developed to the point that early-phase clinical trials in kidney transplantation are now feasible. Cell-based therapies represent a radical departure from conventional treatment, so what grounds are there for this new approach? This article offers a three-part justification for trialing cell-based therapies in kidney transplantation: first, a clinical need for alternatives to standard immunosuppression is identified, based on the inadequacies of calcineurin inhibitor-based regimens in preventing late allograft loss; second, a mechanistic explanation of how cell-based therapies might address this clinical need is given; and third, the possible benefit to patients is weighed against the potential risks of cell-based immunosuppressive therapy. It is concluded that the safety of cell-based immunosuppressive therapy will not be greatly improved by further basic scientific and preclinical development. Only trials in humans can now tell us whether cell-based therapy is likely to benefit kidney transplant recipients, but these should be conservative in design to minimize any potential harm to patients.

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Immunological reactivity against a foreign transplant is governed by many factors, the most fundamental of which are allograft antigenicity and the activity of alloreactive effector T cells.[1] Consequently, current strategies to prevent kidney transplant rejection revolve around donor–recipient tissue-type matching[2] and immunosuppressive drug treatments that primarily target T cells.[3] This basic strategy is tremendously successful, as overall outcomes of modern kidney transplantation attest.[4] What possible incentives might there be to adopt alternative approaches to the care of kidney transplant recipients? This article argues that allospecific regulatory T-cell responses have a greater role in preventing immunological reactivity against allografts than generally appreciated, even under calcineurin inhibitor (CNI)-based immunosuppression. Crucially, developments in the field of cell-based therapeutics mean that clinically applicable treatments to promote immunoregulatory responses are now available that might benefit transplant recipients by reducing their dependence on maintenance immunosuppression or preventing chronic immunological graft injury.[5] Hence, the transplant community is now faced with an important question: should this exciting new technology be embraced or do its risks outweigh the projected benefits?

The answer to this question is controversial. Opinion among transplant immunologists is divided about the clinical feasibility and value of cell-based immunosuppressive therapy. On one side of the debate, promoting immunological regulation is considered an unproven therapeutic principle and cell-based treatments are considered too impractical and inconsistent for routine application. On the other side, induction of immunological regulation is seen as the most credible alternative to general immunosuppressive treatment, which is inescapably toxic and poor at controlling chronic alloimmune reactions.[6] Given the present lack of conventional drugs to enhance regulatory responses, advocates see cell-based therapy as a promising way of establishing allospecific regulation in patients, and hence improving long-term transplant outcomes.[7] This debate has become highly polarized because high-dose conventional immunosuppression, in particular CNI-based regimes and interleukin 2 receptor (IL-2R) blockade, antagonizes regulatory T-cell responses;[8] therefore, most proponents of cell-based therapy favor minimization or withdrawal of CNI or the use of mammalian target of rapamycin mTOR inhibitors. Finding a consensus approach that allows cell-based

therapies to be trialed in a safe, but potentially efficacious immunosuppressive context, is a priority of the *The ONE Study* initiative (www.onestudy.org). With trials of immunoregulatory cell therapies commencing soon, this article seeks to justify these clinical studies.

CLINICAL NEED FOR ALTERNATIVES TO CONVENTIONAL IMMUNOSUPPRESSION

Most patients undergoing kidney transplantation receive standard initial immunosuppressive treatment comprising basiliximab induction, corticosteroids, tacrolimus, and mycophenolate mofetil. Subsequently, whether or not steroids are withdrawn, tacrolimus and mycophenolate mofetil then constitute the mainstay of their long-term maintenance immunosuppression. It is now generally accepted that such regimens are effective at preventing acute rejection episodes, so afford excellent short-term outcomes, but do not prevent chronic renal graft dysfunction.[9] It is this late, progressive, and irreversible allograft damage that cell-based immunosuppressive therapies aim to mitigate.

The pathological processes leading to chronic renal allograft injury are still contested.[10] Chronic CNI nephrotoxicity is often cited as the major cause of late-kidney transplant failure; however, others claim that immunological processes are principally responsible.[11] Whichever mechanism is more important, three points are generally accepted. First, CNIs cause afferent arteriolar vasoconstriction that results in an acute reversible impairment of glomerular filtration and tubular function; in consequence, minimizing CNI dosing improves renal function, at least in the short term. Second, although intensive CNI-based immunosuppression might hinder chronic alloresponses, it does not ultimately prevent late transplant dysfunction and loss. Third, an unwanted effect of CNI treatment is inhibition of regulatory T-cell development and propagation, which might otherwise help control chronic rejection. Arguably then, if there were a nontoxic and effective means of suppressing chronic alloimmune responses, minimization of CNI treatment might favor transplant survival either by avoiding chronic nephrotoxicity or by permitting graft-protective regulatory responses or both. There has been great interest in CNI avoidance strategies in kidney transplantation, notably substitution of CNI by mTOR inhibitors or long-term costimulatory blockade.[12] Regrettably, although such alternatives to CNI-based immunosuppression preserve renal allograft function in the short term, their use has often been associated with higher rates of acute rejection.[13]

This leads us to the proposition that cell-based therapies might prove useful in safely establishing kidney transplant recipients on low-dose tacrolimus-based immunosuppression. Clearly, the suggestion that cell-based regulation-inducing therapies could facilitate tacrolimus dose reduction relies upon three major suppositions, none of which are uncontroversial. First, it supposes a balance exists between graft-damaging effector and graft-protective regulatory responses that can be altered by administration of regulatory cells to a patient. Second, it supposes that there is a dose of tacrolimus capable of suppressing effector T-cell responses without blocking regulatory responses. Third, it supposes that regulatory responses can prevent chronic alloimmune responses, thereby improving long-term allograft survival.[14] To make a convincing case for cell therapy as an adjunct to tacrolimus-based immunosuppression, the validity of each of these suppositions must be proven.

TRANSFER OF IMMUNE REGULATORY FUNCTION AS A THERAPEUTIC CONCEPT

Administering cells with immunoregulatory function to patients to control unwanted immune reactions is not a new proposition. From the earliest discovery that transferring regulatory cells from tolerant to nontolerant animals could establish tolerance in the recipient, it was suggested that the same principle could be applied therapeutically in humans.[15] However, while adoptive transfer became a common experimental practice, its translation to the clinic met many obstacles, not least the difficulty of identifying and isolating human regulatory cells. Despite the substantial challenges it presents, cell-based immunoregulatory therapy remains an attractive alternative to general immunosuppressive therapies for two main reasons. First, cell therapy approaches offer the possibility of inducing *antigen-specific* immunological nonresponsiveness. Second, as peripheral regulation is a self-reinforcing state,[16] it is possible that cell-based immunoregulatory treatments could have very long-lived effects that would not necessarily be limited by the life span of the therapeutic cells.

Definitions of transplantation tolerance

In the normal course of events, were it not for general immunosuppression, allospecific effector T-cell responses occurring after transplantation would normally cause graft-destructive acute rejection. In experimental animals, but only exceptionally in human transplant recipients, acute rejection responses can be silenced and regulatory responses can be strengthened to such an extent that a normally immunocompetent recipient will accept an allograft without ongoing immunosuppression: in this case, a recipient is said to be *tolerant* of the allograft.[17] For a long time, immunologists regarded transplant tolerance as a definite, dominant, and self-perpetuating state that is qualitatively different from, and mutually exclusive with, opposing states of nontolerance. Yet, this view is becoming increasingly difficult to reconcile with our developing understanding of the cellular mechanisms of peripheral regulation. Specifically, a 'quantitative' account of transplant tolerance is now emerging, which holds that immunological reaction or nonreaction to an allograft is dictated by the net balance of effector cell and regulatory cell responses, and not by mechanisms unique to the tolerant state. This dynamic balance is perhaps best understood as a competition between effector and regulatory mechanisms.

Controlling the balance between effector and regulatory responses to suppress or abrogate alloreactivity is now a major