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INVITED COMMENTARY

More on risk/benefit ratio of anti-IL-2 receptor monoclonal antibodies

Jean-Paul Soulillou and Diego Cantarovich

Departments of Nephrology and Clinical Immunology, Transplantation, ITUN, Nantes University Hospital, Nantes, France

Correspondence
Jean-Paul Soulillou MD, Departments of Nephrology and Clinical Immunology, Transplantation, ITUN, Nantes University Hospital, Nantes, France. Tel.: 33 240 08 74 10; fax: 33 240 08 74 11; e-mail: jean-paul.soulillou@univ-nantes.fr

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Acute rejection arises when alloreactive T-cells infiltrate the graft. A critical step in the activation of these cells is the expression of the high affinity interleukin-2 receptor, which induces rapid proliferation of T-cells when interleukin-2 binds to it. The IL2-R consists of three transmembrane protein chains: α (CD25), β (CD122), and γ (CD132). CD25 does not transduce a signal, but associates with CD122 and CD132 to form the receptor that triggers signaling [1]. Clinically efficient anti-IL2-R are directed at the α chain and disturbs the IL-2 high affinity site.

A first human trial with a murine anti-IL2-R named 33B3.1, initiated in the middle 1980s, suggested the efficacy of monoclonal antibodies against IL-2 high affinity receptor in decreasing acute rejection episodes as well as a good clinical tolerance [2]. In a first randomized comparison of a nonmodified antibody with polyclonal antithymocyte globulin (ATG) induction, the use of this murine anti-IL2-R was followed by a similar incidence of acute rejections with 70% of patients being rejection-free within the first year post-transplant [3]. The benefit of anti-IL2-R induction was ultimately demonstrated in a large pivot study using a chimeric antibody [4]. The same results were subsequently confirmed in prospective randomized studies including high-risk recipients of renal retransplant [5] and simultaneous pancreas–kidney transplant [6]. These agents represent, with ATG, one of the most popular induction strategies used after renal transplantation.

Lim *et al.* in this issue retrospectively analyzed from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), the long-term (i.e. 5 years) benefits of anti-interleukin-2 receptor monoclonal antibody (anti-IL-2R) induction after all types of renal transplantation. From 2000 to 2006, 1470 patients received IL2-R induction and 1874 patients did not. Maintenance immunosuppression included calcineurin inhibitors (CNI), mycoplenolate mofetil, azathioprine, rapamycin, and steroids. The use of anti-IL2-R was associated with significantly less acute rejection episodes (although the incidence was 20%), improved graft function at 5 years (but not of graft survival) and a similar risk of adverse events, including malignancy-induced death [7].

In the absence of randomized studies focused on long-term end-points such as chronic rejection, malignancies, graft survival, patient survival etc. the balance between efficacy, safety, and cost is difficult to ascertain. Only retrospective analyses of large cohorts from national or international registries are able to identify predictive factors with potential direct effects on these crucial long-term endpoints. The term induction was introduced in the 1960s when ATG was initially given from the day of

transplantation and sometimes prolonged for several months after. The main goals of induction are to prevent rejection and to allow minimization of maintenance immunosuppression such as steroid-free and/or CNI-free. However, induction should not induce more infectious episodes and/or malignancies. Although not analyzed by Lim *et al.*, induction with anti-IL2-R may benefit the association of a decrease in the amount of immunosuppression to prevent in the long-term (i.e. more than 5 years) the occurrence of severe adverse events.

Long-term graft acceptance maybe in part mediated by T regulatory cells. Regulatory T-cells (Treg) are critical to the maintenance of immune cell homeostasis as evidenced in humans by the severe consequences of genetic alteration of Treg population. In animal models, Treg cells maintain order in the immune system by enforcing a dominant negative regulation on other immune cells. Broadly classified into natural or adaptive (induced) Treg; natural Treg are $CD4^+$, $CD25^+$, CD127low, $FOXP3^+$ T-cells which develop, and emigrate from the thymus to perform their key role in immune homeostasis. Adaptive Treg are nonregulatory $CD4^+$ T-cells which acquire CD25 (IL-2Rα) expression outside of the thymus, and are typically induced by inflammation and disease processes, such as autoimmunity and cancer. Precise understanding of the immunosuppressive mechanism of Treg cells, which particularly must be well distinguished from activated CD25 positive cells, remains elusive [8]. Treg manifest their function through several mechanisms that include the secretion of immunosuppressive soluble factors such as IL-9, IL-10, and TGF-β, cell contact mediated regulation via the TCR and other costimulatory molecules, such as CTLA-4, GITR, and cytolytic activity. Of interest, patients with chronic rejection have lower amount of circulating Treg [9].

Whether anti-IL2-R induction negatively or positively impacts the function of Treg remains unclear. Both IL-2 and CD28-CD80/CD86 signaling are critical for $CD4^+$ $CD25^+$ $FOXP3^+$ Treg survival [10]. Both Belatacept (a fusion protein composed of the Fc fragment of a human IgG1 immunoglobulin linked to the extracellular domain of CTLA-4) and Basiliximab (an anti-CD25 monoclonal antibody) are among the arsenal of current immunotherapies used in kidney transplant patients. The combined Belatacept/Basiliximab therapy has no long-term effect on circulating Treg when compared with CNI [10]. Basiliximab caused a transient loss of both $FOXP3^+$ and $FOXP3^-$ $CD25^+$ T-cells in the circulation raising questions about the use of this therapy in tolerance promoting therapeutic protocols.

Without doubt, anti-IL2-R induction has a high benefit/risk ratio in preventing acute rejection following renal transplantation and probably this early result influences long-term results.

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