Integrin antagonists for transplant immunosuppression: panacea or peril?

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Despite a drought of innovation that has afflicted the transplant drug pipeline over the previous decade, the recent success of belatacept (a novel CD28 antagonist) in phase III clinical trials may soon usher in a new era of transplant immunosuppression regimens that are designed around protein-derived “biologics.” The initial wave of these transplant biologics will likely target essential costimulatory molecules required for T cell activation, such as the CD28-B7 interaction disrupted by belatacept. However, a growing body of both experimental and clinical literature has highlighted the role that adhesion molecules such as integrins may serve as additional therapeutic targets for transplant immunosuppression. While integrin blockade potentially holds much promise for the transplant field, enthusiasm for its adoption must be tempered by a reasonable consideration of its risk profile.

These integrins are heterodimeric cell surface receptors found on a variety of immune cells, including T cells, B cells, macrophages and neutrophils. Integrins mediate adhesion between these immune cells and other cells in their environment, playing vital roles in both leukocyte activation and trafficking to sites of inflammation. Two prototypic integrins are LFA-1 (leukocyte function-associated antigen-1, an \( \alpha L\beta 2 \) integrin) and VLA-4 (very late antigen-4, an \( \alpha 4\beta 1 \) integrin). LFA-1 in particular has been shown to play a vital role in the formation of an immunological synapse between T cells and antigen presenting cells (APCs). Both LFA-1 and VLA-4 have also been implicated in the “arrest” of rolling lymphocytes at sites of inflammation and the subsequent transendothelial migration of T cells into this inflamed tissue. These immunomodulatory properties of integrins spurred the clinical development of integrin antagonists against both LFA-1 (efalizumab) and VLA-4 (natalizumab) to treat various autoimmune diseases. Specifically, efalizumab was approved by the FDA for the treatment of psoriasis and natalizumab has found use in both multiple sclerosis and Crohn’s disease patients.
While the initial clinical applications of integrin blockade were focused on autoimmunity, multiple experimental and even clinical trials have emerged over the last decade supporting the use of these therapies in the clinical realm of transplantation. Monotherapy with either LFA-1 or VLA-4 antagonists proved efficacious in prolonging graft survival in a variety of murine transplant systems, including skin [4], cardiac [5] and islet [6,7] allograft models. In addition to suppressing acute rejection, integrin blockade was also found to diminish chronic rejection in a murine model of cardiac allograft vasculopathy [8]. Combined integrin blockade with both anti-VLA-4 and anti-LFA-1 demonstrated potent synergy in a murine islet transplant system, with islet grafts lasting >60 days compared to 7–9 days with integrin antagonist monotherapy [9]. To further augment the efficacy of integrin blockade, several investigators coupled it with standard costimulatory blockade drugs such as anti-CD154 or CTLA-4 Ig, achieving prolonged graft survival in a variety of murine transplant systems [10,11]. Dual integrin/costimulatory blockade was even shown to prolong survival of xenografts such as porcine islets in murine recipients [12]. This regimen of dual costimulatory and integrin blockade was also recently utilized successfully in a primate islet transplant system (using belatacept and efalizumab), demonstrating a substantial prolongation in islet graft survival [13]. All of these encouraging preclinical studies established the critical groundwork that informed later human clinical trials with these integrin antagonists for transplantation.

The initial clinical trials of LFA-1 antagonists in transplantation utilized a mouse anti-human CD11a monoclonal antibody (odulimomab); small pilot studies with this monoclonal were mixed, but at least one study demonstrated that induction therapy with odulimomab was as effective as rabbit anti-thymocyte globulin in preventing acute rejection [14]. Subsequent multicenter trials utilized efalizumab, a fully humanized IgG1 anti-LFA-1 monoclonal antibody. In one early multicenter trial, patients were randomized to either high (2 mg/kg) or low (0.5 mg/kg) dose efalizumab in new renal transplant recipients who were treated with either half-dose cyclosporine/sirolimus/prednisone or routine cyclosporine/MMF/prednisone immunosuppression regimens [15]. Despite using half-dose cyclosporine and sirolimus, the cumulative rejection rates with these efalizumab-based regimens (10.4%) were comparable to historic controls with full-dose calcineurin inhibitor-based regimens. However, in the subset of patients receiving the high dose of efalizumab coupled with conventional full-dose cyclosporine/MMF/prednisone, almost 30% of patients developed post-transplant lymphoproliferative disease, a concerning development (of note, none of the patients treated with either low-dose efalizumab regimens or high-dose efalizumab with half-dose conventional agents developed PTLD in this study). More recently, efalizumab was used successfully by two different groups to promote engraftment and insulin-independence in recipients of islet transplants from single donors [16,17].

While the initial clinical experience with integrin antagonists to treat autoimmune diseases was highly encouraging, early enthusiasm for these drugs was eventually tempered by the occurrence of progressive multifocal leukoencephalopathy (PML) in several patients receiving chronic treatment with these drugs [18,19]. PML is an opportunistic viral infection resulting from reactivation of latent JC virus (a human polyomavirus) in the brain of immunosuppressed patients [18]. PML is highly lethal, with most patients succumbing to disease after it has developed. The risk of these biologics was first revealed in patients
chronically treated with natalizumab, a very small handful of whom began to manifest clinical signs of PML. Importantly, the risk of PML is almost solely confined to those patients receiving long-term integrin blockade, with patients receiving at least 18 monthly infusions of natalizumab estimated to have a 1:1000 risk of developing PML [18]. The PML risk signature of natalizumab initially led to its voluntary withdrawal from the market, but vocal support from multiple sclerosis patients led to the reintroduction of natalizumab under tight controls in June 2006. As of July 2010, a total of 61 patients on natalizumab have developed PML [19].

Similar to natalizumab, efalizumab also is associated with an elevated risk of PML and JC virus reactivation. Of the estimated 46,000 patients who had been treated with efalizumab worldwide since its FDA approval in 2003, a total of four PML cases (three definite and one probable) were reported by 2009, yielding a total PML incidence of 1 in 10,000 [18]. However, of those patients treated for >3 years with efalizumab (which included every patient who developed PML), the estimated incidence rate was 1 in 400 patients [18]. On April 8, 2009, Genentech announced that they would voluntarily withdraw efalizumab from the market due to this PML risk, and efalizumab was phased out completely by June 2009.

While a remote risk of developing a fatal neurodegenerative condition may be utterly unacceptable for patients with a relatively benign condition such as psoriasis, it may certainly be tolerable in the transplant arena, especially if the novel integrin blockade therapy prolongs allograft function compared to conventional immunosuppression. The argument for exploring transplant indications for integrin antagonists is further bolstered by the fact that many drugs currently used to treat transplant patients (such as mycophenolate mofetil and rituximab) actually carry similar risks for PML compared to either natalizumab or efalizumab [18,20]. Furthermore, the likely duration of therapy for integrin antagonists used in a transplant setting would likely prove protective against PML development. The epidemiology of PML in patients with autoimmune diseases treated with integrin antagonists confirms that the risk of PML increases substantially with duration of therapy: the incidence of PML is 0.01 per 1000 patients for those who received 1 to 12 infusions of natalizumab, 1.27/1,000 for those who received >12 infusions and 1.71/1,000 in those who received >24 infusions [19]. Integrin antagonists would likely be employed as short-term perioperative induction immunosuppression therapy in transplant patients, which should substantially mitigate the risks posed by integrin blockade.

Thus, the clinical calculus of risk versus benefit for integrin antagonists differs dramatically when applied to organ transplantation compared to their initial indications for autoimmunity. Given the encouraging preclinical and clinical trial data, perhaps the time has come to re-evaluate the potential applications of integrin blockade (such as VLA-4 and LFA-1 antagonists) for organ transplantation. Future clinical trials, perhaps studying regimens incorporating induction therapy with integrin antagonists and maintenance therapy with belatacept, certainly seem not only justified but indeed essential to fully clarify the efficacy and safety of integrin antagonists for transplantation.
References


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