Studies Investigating Pretransplant Donor-Specific Blood Transfusion, Rapamycin, and the CD154-Specific Antibody IDEC-131 in a Nonhuman Primate Model of Skin Allograft Rejection


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Studies Investigating Pretransplant Donor-Specific Blood Transfusion, Rapamycin, and the CD154-Specific Antibody IDEC-131 in a Nonhuman Primate Model of Skin Allotransplantation


Anti-CD154 variably prolongs allograft survival in nonhuman primates. Rodent studies suggest that adding pretransplant donor-specific transfusion (DST) and/or rapamycin to anti-CD154 improves survival. The CD154-specific Ab IDEC-131 was tested alone and in combination with rapamycin for its ability to inhibit rhesus MLRs. The ability of the Ab to block endothelial activation was also assessed. IDEC-131 was then tested alone and in combination with DST and/or rapamycin for its ability to prevent rejection of full-thickness, MHC-mismatched rhesus skin allografts. Animals were monitored for donor-specific hyporesponsiveness by MLR and alloantibody determination. IDEC-131 modestly inhibited rhesus MLRs and inhibited CD154-dependent endothelial cell activation. Rapamycin combined with IDEC-131 additively inhibited MLRs. IDEC-131 modestly prolonged allograft survival when compared with no treatment, rapamycin alone, or DST plus rapamycin. Adding DST to IDEC-131 did not prolong survival beyond IDEC-131 alone. IDEC-131 plus rapamycin was effective in prolonging graft survival, although animals had episodes of acute rejection before graft demise. Therapy with IDEC-131, rapamycin, and DST induced long-term allograft survival without intermittent acute rejection. However, no evidence for MLR inhibition was seen, and most animals eventually developed alloantibody. All animals ultimately rejected their grafts after drug withdrawal. IDEC-131 modestly prolongs rhesus skin allograft survival. Rapamycin and rapamycin plus DST improve the efficacy of IDEC-131 in prolonging allograft survival. IDEC-131, rapamycin, and DST are a promising combination for clinical evaluation in allotransplantation. The Journal of Immunology, 2003, 170: 2776–2782.

D espite significant advances in the field of allotransplantation, patients still require nonspecific, toxic, and costly immunosuppressive therapy to prevent rejection. These drugs, typically a combination of a calcineurin inhibitor (e.g., cyclosporine), an antiproliferative agent (e.g., mycophenolate mofetil), and glucocorticosteroids, effectively limit acute rejection, but also increase the incidence and severity of many infections, and other physiological and malignant complications. Ag-specific immunomodulatory methods are therefore being investigated, as they are thought to be potentially better tolerated and more durable than generalized immunosuppression. Several groups have tested various costimulatory receptor-based agents as potential components of an Ag-specific approach (reviewed in Ref. 2). Although costimulatory receptor-based therapies have prevented allograft rejection in several animal models, long-term survival has been inconsistently achieved in primates (3–9). Studies evaluating whether other agents might synergize with costimulatory pathway reagents have generally found that many standard immunosuppressants actually decrease the effectiveness of costimulatory pathway-based strategies (4, 10–12).

Anti-CD154 Abs have been particularly efficacious in preventing allograft rejection in rodents (10–15) and primates (3–7, 9). CD154 is up-regulated transiently on T cells early after activation (16) and serves as the ligand for CD40 expressed on primed APCs. The reciprocal interplay between the two receptors plays an important role in initiating and regulating both APC and T cell activation. Previous studies have shown that interactions between T cell CD154 and CD40 expressed on endothelial cells can also induce endothelial cell activation manifest by up-regulation of cell adhesion molecules such as E-selectin and ICAM (17, 18). The effects of anti-CD154 Abs on activated T cells, endothelial cells, and APCs are believed to mediate the allograft-promoting effect (19). We have previously investigated the humanized CD154-specific Ab hu5C8 in primate allograft models (3, 4, 7, 9). Although promising in preclinical trials, its use has been limited by thrombotic complications seen in early human trials (20). Another humanized CD154-specific agent, IDEC-131, has been studied in clinical trials recently (21), but IDEC-131 has not been extensively studied in preclinical transplant models.

Rodent studies have demonstrated that the combination of pretransplant donor-specific transfusion (DST)3 plus anti-CD154 generally prolongs rejection-free survival (13–15, 22). Similarly, rodent studies have shown that rapamycin plus anti-CD154 syn-

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3 Abbreviations used in this paper: DST, donor-specific transfusion; HEC, human endothelial cell.
ergistically prolongs allograft survival, presumably by promoting activation-induced T cell death (11). Nevertheless, while the rodent data are encouraging, rodent transplant models are generally regarded as being overly permissive as predictors of therapies designed to support human allograft survival. Specifically, DST or rapamycin alone have been successful in inducing indefinite allograft survival in some rodent strains. This study was designed to evaluate the efficacy of the CD154-specific Ab IDEC-131, alone and in combination with DST and/or rapamycin, in a rigorous model of allotransplantation: full-thickness skin transplantation in MHC-mismatched rhesus monkeys. The specific goal was to develop a clinically applicable therapy that could be used to prevent human allograft rejection. We reasoned that because both DST and rapamycin are in clinical use, they could be fairly easily studied in combination with an investigational agent such as IDEC-131.

Materials and Methods

Abs and reagents

The humanized CD154-specific mAb, IDEC-131, was provided by IDEC Pharmaceuticals (San Diego, CA). The following Abs were used for flow cytometry: FITC-labeled mouse anti-monkey CD3 PE (FN18; BioSource, Camarillo, CA), goat anti-monkey IgG FITC, goat IgG FITC isotype control (Kirkegaard & Perry Laboratories, Gaithersburg, MD), mouse anti-human CD62E FITC (Serotec, Raleigh, NC), mouse isotype control IgG1 FITC, and IgG1 PE (BD Biosciences, San Diego, CA). Human rTNF-α produced in Escherichia coli was purchased from R&D Systems (Minneapolis, MN). Rapamycin was purchased from Wyeth (Philadelphia, PA).

Cell culture and in vitro assessments of IDEC-131 and rapamycin effects

The ability of IDEC-131 to inhibit CD154-mediated cellular interactions was studied in two in vitro cell culture systems, a human T cell CD154-mediated endothelial cell activation assay and a nonhuman primate MLR.

Human endothelial cells (HEC) were isolated from cadaveric aorta by digestion with 0.01% collagenase. After a wash with RPMI 1640 medium (Life Technologies, Grand Island, NY), primary cultures and subcultures of HEC were established in endothelial cell culture medium (Life Technologies) supplemented with 10% FCS (HyClone Laboratories, Logan, UT), and verified to be endothelial cells by determination of von Willebrand factor expression using flow cytometry. The CD154-expressing human T cell line D1.1 was purchased from American Type Culture Collection (Manassas, VA). This CD4-negative line is capable of providing CD154 contact-dependent helper functions in vitro (23). Cultures were established and maintained at 1 × 10^6 cells/ml in RPMI 1640 medium containing 10% FCS, penicillin, and streptomycin. The D1.1 cells were characterized for surface Ag expression by flow cytometry using the following mouse mAbs: CD4 PE, CD62E PE, CD80 PE, and CD54 PE (BD Biosciences).

HEC were transferred into 12-well tissue culture plates and grown to confluence. D1.1 cells were washed twice with RPMI 1640 medium and then diluted at 2.5 × 10^5 cells/ml with culture medium. D1.1 cells (5 × 10^5) were added to wells containing HEC monolayers in the presence or absence of 100 μg/ml of IDEC-131 or a humanized isotype control (h1f1; Genetics Institute, Andover, MA). Cocultures were conducted at 37°C for 48 h. Resting HEC and HEC activated by human rTNF-α (at 250 U/ml for 2 h) were used as negative and positive controls, respectively.

One-way MLRs using thymus responder-stimulator pairs were performed using freshly isolated PBMC responders co-cultivated with mitomycin-C-treated stimulators (1 × 10^6, responder to stimulator ratio 1:1; also freshly isolated PBMC) at 37°C for 5 days. Stimulator cells were treated with mitomycin C (50 μg/ml) for 38 min, followed by three washes with PBS before their addition to the MLR. Responder and stimulator cells were procured for pretransplant MLR before the initiation of any therapy, and cells procured for posttransplant study were taken from animals that had finished all immunotherapy and cleared their therapeutic agents. Cells were pulsed with 1 μCi of [3H]thymidine during the final 24 h of culture and harvested onto a pressed fiberglass paper. Lymphocyte proliferation was measured by [3H]thymidine incorporation using a beta liquid scintillation counter. IDEC-131 and/or rapamycin were added at various concentrations. When both drugs were used, the IDEC-131 dose was held constant at 50 μg/ml and the rapamycin dose was varied.

Donor:recipient pair selection

Outbred rhesus monkeys, 2-5 years of age, seronegative for SIV and herpes B, were obtained from LABS of Virginia (Yemassee, SC) and used as donors and recipients. The experiments described in this study were conducted according to the principles set forth in the “Guide for the Care and Use of Laboratory Animals,” Institute of Laboratory Animals Resources, National Research Council, Department of Health and Human Services, Publication (National Institutes of Health) 86-23 (19850). The selection of donor-recipient pairs was based, as previously described (6), upon genetic nonidentity at MHC class I and II, as well as by pretransplantation reactivity in MLR. MLRs were performed for each recipient against all MHC genotype-mismatched potential donors, and the highest responder pair was then selected as reciprocal donor and recipient.

Skin transplants

Animals were anesthetized with i.m. ketamine (10 mg/kg) and xylazine (0.6 mg/kg) and redosed as needed. Full-thickness abdominal skin grafts were harvested onto a pressed cotton bolster. Donor skin grafts were sutured into recipient wounds at the site of delayed donor-host skin matching, with simple interrupted sutures with hair follicles pointing opposite the native skin follicles for later ease in identifying grafted from normal skin sites. Cotton bolsters were placed on top of the grafts and a dressing was applied. The animals were then placed in jackets to protect the grafts. Dressings were changed on posttransplant day 7, and sutures were removed on posttransplant day 9.

Immune therapies and experimental groups

IDEC-131 was administered i.v. over a 60-min period. We tested IDEC-131 and rapamycin at two doses (Table I). The lower dose induction regimen consisted of IDEC-131 (15 mg/kg/dose) given on day 0 (during the skin-grafting procedure); on posttransplant days 1, 3, and 7, and then weekly for 8 wk. Selected recipients undergoing lower dose induction therapy were treated with oral rapamycin at a dose of 1 mg/kg/day for 2 wk, beginning the day of transplantation, with a subsequent dose reduction to 0.5 mg/kg/day given for an additional 6 wk. The higher dose induction regimen consisted of IDEC-131 (20 mg/kg/dose) given on days −1, 0, 3, 7, and weekly for 8 wk. Selected recipients receiving high dose IDEC-131 therapy were given oral rapamycin at a non tapering dose of 1 mg/kg/day for 3 mo beginning the day of transplantation. A single dose (7 ml/kg recipient weight) of heparinized whole donor blood was given to selected recipients in both the high and low dose groups immediately following the initial IDEC-131 infusion. Control animals receiving rapamycin alone were given the drug at 1 mg/kg/day. For all groups, rapamycin was administered based on a prescribed dose rather than a targeted level. Trough levels at 1 mg/kg ranged between 5.2 and 8.5 ng/ml.

We divided the recipients into seven groups (Table I). Group 1 (n = 3) recipients received no treatment. Group 2 (n = 2) recipients were treated with rapamycin alone. Group 3 recipients were treated with low dose (n = 4) and high dose (n = 2) IDEC-131 alone. Group 4 recipients were treated with low dose (n = 4) or high dose (n = 2) IDEC-131 plus rapamycin therapy without DST. Group 5 recipients were treated with low dose (n = 2) or high dose (n = 1) IDEC-131 induction therapy with DST, but without rapamycin. Group 6 (n = 2) recipients were treated with pretransplant DST and rapamycin, but no IDEC-131. Group 7 recipients were treated with low dose (n = 3) or high dose (n = 3) IDEC-131 induction therapy in combination with both pretransplant DST and rapamycin.

Posttransplantation monitoring

Skin grafts were inspected at the time of the initial dressing change (day 7), and then monitored daily. Dermal elasticity was determined by palpation. Serum samples were collected for alloreactive Ab analysis before transplantation, on days 7 and 21, then approximately every 2 mo thereafter. The sera were stored at −70°C until analysis was performed. Recipients with long surviving grafts had blood drawn for MLR assays using both donor and third party fresh PBMC as stimulator cells. Allograft biopsies were performed if the graft became erythematous, as this is typically the case.
first sign of rejection (9). We have previously shown that normal appearing, nonerythematous skin allografts do not have histological evidence of cellular rejection (9). All rejections were confirmed by biopsy. Protocol surveillance biopsies were not performed as the trauma from these procedures was thought to have the potential to influence the course of the rejection. As skin grafts can remain viable despite rejection, two parameters were noted for all grafts. Erythema-free survival was defined as the number of consecutive days posttransplant in which there were no signs of rejection. Total graft survival refers to the number of consecutive days posttransplant in which the graft was viable and without ulceration.

Anti-donor alloantibody assay and MLR

Anti-donor alloantibody was detected by FISH cytometry evaluating the binding of frozen recipient serum Ab to freshly isolated, nonactivated donor CD3+ T cells. Target PBMC were collected after animals were withdrawn from all immunotherapy. Briefly, recipient serum samples were incubated with donor PBMC at 4°C for 30 min. After washing with PBS, the cells were incubated with FITC-labeled goat anti-monkey IgG Ab (Kirkegaard & Perry Laboratories) and PE-labeled anti-thesus CD3 (BioSource) at 4°C for 30 min, then washed twice with flow cytometry buffer. Samples were analyzed on a BD Biosciences FACScan. The response to third party and autologous PBMC served as negative controls.

One-way MLRs were performed in long surviving recipients for evidence of donor-specific hyporesponsiveness following drug withdrawal. Donor PBMC used for MLRs were collected 3–4 mo after immunotherapy withdrawal. To analyze MLRs that were performed at different time points, a stimulation index (SI) was calculated using the formula: SI = cpm stimulated responder cultures/cpm unstimulated cultures.

Histology

All biopsy samples were fixed in 10% neutral-buffered Formalin and paraffin embedded. Fixed skin graft biopsies were prepared and stained with H&E by the veterinary pathology facility on site. Necropsies were performed on all monkeys euthanized after allograft rejection.

Results

**IDEC-131 and rapamycin prevent rhesus monkey T cell proliferation in vitro**

IDEC-131 modestly reduced lymphocyte proliferative responses when used alone in MLR (Fig. 1a). The reduction in proliferation was not dose dependent and was consistent with the action of other anti-CD154 Abs (3). Thus, this human-specific Ab was active in a rhesus system. Rapamycin had a dose-dependent inhibitory effect in the MLR assay (Fig. 1b). IDEC-131 and rapamycin additively inhibited the MLR, with the inhibitory rapamycin effect displaying dose dependence across three log concentrations (Fig. 1c).

**IDEC-131 prevents T cells expressing CD154 from activating endothelial cells in vitro**

To test whether IDEC-131 could prevent contact-dependent CD154-mediated interactions in a manner similar to other humanized CD154-specific Abs, we measured T cell-mediated endothelial cell activation with or without added Ab. Resting HEC (negative control) did not express CD62E, TNF-α-activated HEC (positive control) markedly expressed CD62E. Coincubating HEC with D1.1 cells induced CD62E expression that was completely blocked using IDEC-131, but was not blocked by the humanized isotype control Ab hu1f1 (data not shown).

**Skin allograft survival is prolonged by therapy with IDEC-131 plus rapamycin with and without DST**

The skin allografts placed on monkeys treated with low or high dose IDEC-131 alone survived from 10 to 16 days (mean = 13.3 ± 2.4 days), only slightly longer than untreated recipients (mean = 7.3 ± 0.6 days) (Table I). Rapamycin therapy alone or in combination with pretransplant DST did not prolong allograft survival (mean = 9.5 ± 1.3 days). When given with either the low or high dose IDEC-131 regimen, DST did not improve, and possibly worsened, skin allograft survival (mean = 8.7 ± 0.6 days). In each of the groups mentioned above, rejection advanced rapidly from erythema to edema, ulceration, and necrosis. Histological evaluation of the allograft biopsies was consistent with typical acute skin allograft rejection, as characterized by a prominent dermal lymphocytic infiltrate and pyknotic keratinocytes consistent with apoptosis (data not shown). Notably, IDEC-131 (low or high dose) combined with rapamycin prolonged skin allograft survival up to 45 and 246 days, respectively (low dose mean = 27.3 ± 15.3 days; high dose mean = 165 ± 114.5 days), although all recipients’ grafts displayed an apparent early acute rejection episode. Although the skin allografts remained viable, they were clearly not normal in appearance following the rejection episode (Fig. 2). Histological evaluation confirmed a typical lymphocytic infiltration in these grafts (not shown).

The combination of DST plus IDEC-131 and rapamycin extended the erythema-free survival period (low dose mean = 52.7 ± 37.9 days; high dose mean = 142.7 ± 117.4 days) when compared with IDEC-131 therapy alone or IDEC-131 in combination with rapamycin. We observed no evidence of skin allograft rejection in two of three monkeys given high dose IDEC-131 with DST and rapamycin throughout their immunotherapy treatment (Table I). Rejection ensued 95–143 days after stopping therapy (Fig. 3). When the skin allografts were rejected by these animals, the response appeared to be consistent with the typical acute allograft rejection observed in the other groups. The one animal in the high dose IDEC-131 plus DST and rapamycin group that rejected...
its skin allograft early was retrospectively shown to be ABO incompatible with the donor (B to O). All other animals were confirmed to be ABO compatible.

We attempted to rescue a rejecting skin allograft in one animal given high dose IDEC-131 plus DST and rapamycin at the first sign of rejection (erythema) at day 185 (95 days after therapy withdrawal). IDEC-131 was readministered after the skin was biopsied and rejection was confirmed. The therapy was ineffective in reversing the rejection episode, and the graft was lost by day 202.

We observed no apparent toxicity of the therapies used. Specifically, no animal developed an infection or other unexplained illness, and no animal displayed symptoms or signs of any thromboembolic events. Similarly, necropsy on animals that received IDEC-131 showed no occult pathology. Specific attention was

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**FIGURE 1.** The effect of IDEC-131 alone or in combination with rapamycin on rhesus monkey MLR. IDEC-131 alone (A) results in limited inhibition of lymphocyte proliferation. Increasing concentrations of rapamycin lead to progressive inhibition of lymphocyte proliferative responses (B). There is an additive effect of the combination in blocking lymphocyte proliferation in MLR (C).
directed toward the lungs and pulmonary arteries, and no subclinical pulmonary emboli were detected.

**IDEC-131 therapy in combination with rapamycin and/or pretransplant DST fails to induce donor-specific MLR hyporeactivity**

As indicated in Materials and Methods, donor-recipient pairs were selected, in part, on the basis of a strong MLR proliferative response. We tested recipient antidonor (and third party) MLR responses posttransplant in those recipients with long-surviving normal allografts after immunotherapy was withdrawn. We found no evidence for donor-specific hyporesponsiveness in these animals. All recipients treated with IDEC-131 and rapamycin with or without DST maintained a strong proliferative response to their donors and to third party cells when compared with pretransplant MLR. Even the two longest surviving animals maintained responsiveness as vigorous as that seen pretransplant (Fig. 4).

**IDEC-131 therapy in combination with rapamycin and/or pretransplant DST fails to prevent the eventual formation of donor-specific alloantibody**

Serum samples were obtained from recipients before transplantation and contained no detectable alloreactive Ab directed toward donor CD3+ T cells. Technically successful serial alloantibody determinations were made in 18 animals. Both animals receiving rapamycin alone developed alloantibody within the first week posttransplantation. Four of six animals that received IDEC-131 developed alloantibody at the time of allograft rejection. All animals receiving IDEC-131 and rapamycin developed alloantibody, although the two animals with the longest graft survival had delayed onset of Ab formation beyond 45 days. Likewise, the two animals studied that were treated with IDEC-131, DST, and rapamycin with the longest survival did not develop detectable alloantibody until greater than 150 days posttransplantation. Thus, although some animals appeared to have delayed onset of alloantibody formation, even long surviving animals typically developed donor-specific alloantibody (not shown). Thus, as with the cellular reactivity as measured by MLR, there was no evidence of humoral immune tolerance in these animals.

**Discussion**

We report that therapy with the humanized CD154-specific Ab IDEC-131 combined with rapamycin with or without pretransplant DST delays acute cellular rejection in a rigorous nonhuman primate model of skin transplantation. Indeed, two recipients treated with IDEC-131 plus rapamycin and DST displayed no signs of allograft rejection and remained alloantibody free for several months following the cessation of therapy. Although the best outcomes were seen in the two animals treated with this combination...
therapy, the small numbers in this trial prohibit a clear determination of the relative contributions of rapamycin and DST. Nevertheless, the use of either rapamycin or rapamycin plus DST clearly improves upon the efficacy of anti-CD154 alone, and is thus deserving of more extensive analysis in models of vascularized allograft transplantation.

Although anti-CD154-based therapies have been investigated in numerous models, and have generally shown great potential as agents for preventing transplant rejection, early clinical experience with this approach has been much less impressive (20). The disparate experimental and clinical results may be due to many factors, including variations in the Ab preparations given, differences in the sensitivity to therapy between the different species, and pre-existing disease that may have existed in the clinical setting, but not in the preclinical models (e.g., atherosclerosis, cross-reactive viral immunity). It is clear, however, that the optimal use of CD154-specific Abs is yet to be determined. Studies examining adjuvant immune therapies to pair with CD154-directed therapy thus remain paramount in understanding how to apply this approach clinically.

In the present study, we examined whether adjuvant therapy with rapamycin and DST might improve the efficacy of anti-CD154, specifically looking toward a clinically applicable therapy for future human trials. One serious concern associated with simply adding immunosuppressive agents to an anti-CD154-based regimen is that nonspecific immunosuppressive agents appear to attenuate the anti-CD154 efficacy (4, 10–12). Specifically, studies have consistently found that both calcineurin inhibitors and steroids attenuate the efficacy of anti-CD154. Given that these agents represent standard-of-care approaches in modern antirejection therapy, early transplant trials have been forced to add anti-CD154 to existing antirejection therapies, thus potentially masking the agent’s effect. Furthermore, CD154-specific Abs performed so well in vascularized allograft models that synergy was difficult to identify. Anti-CD154 monotherapy was nearly completely effective in preventing acute rejection following renal transplantation, prohibiting the identification of additional salutary effects from adjuvant therapy. We have thus begun to study skin allografts. This model represents an extraordinarily rigorous one that may offer more opportunities to identify synergistic effects of additional agents.

Rodent studies have generally suggested that both DST and rapamycin improve anti-CD154-specific Ab efficacy. In rodent models, however, these agents alone often induce tolerance. Our study is the first to demonstrate in a primate that CD154-directed therapy can be improved by the use of rapamycin and DST. These data provide preclinical evidence suggesting an avenue for testing CD154-specific Ab-based regimens in the clinic.

Despite the effectiveness of the combination therapies, we found no evidence that tolerance was induced. This was indicated by the unaltered MLR responsiveness, the eventual formation of alloantibody, and even more definitively by eventual allograft rejection. Other studies have suggested that a regenerating donor Ag source such as bone marrow or peripherally mobilized stem cells may achieve tolerance, and others have shown that CD154 fits well with other conditioning regimens designed to create mixed chimerism (24, 25). Studies using vascularized grafts may also improve anti-CD154-based approaches, as these grafts are more readily accepted.

The therapy outlined in this trial fits well with emerging theories shaping the development of protolerant immune modulation. It targets APC activation by theoretically limiting the interplay between T cell-derived CD154 and APC CD40 (26). Through DST, it provides donor Ag in this context of attenuated APC activation, thus encouraging an Ag signal without sufficient costimulation (2). Those T cells that do become activated do so in the presence of rapamycin, and are thus more likely to undergo activation-induced cell death (11). Our results suggest that therapy with IDEC-131 combined with rapamycin perhaps with DST might be useful as a therapy to promote allograft survival in humans.

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