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Therapeutic approach to organ transplantation

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Introduction

Renal transplantation is firmly established as the preferred treatment for many patients suffering from end-stage renal disease. Nonetheless no absolute consensus has developed on how to achieve optimal immunosuppression, and many individual centres employing somewhat different protocols report excellent graft and patient survival. Immunological considerations, including antirejection therapy, are organized around a few general principles.

The first consideration is careful patient preparation and, in the circumstance of living donor renal transplantation, selection of the best available ABO compatible, human leukocyte antigen (HLA) match in the event that several potential living related donors are available for organ donation. Second is a multitiered approach to immunosuppressive therapy similar in principle to that used in chemotherapy; several agents are used simultaneously, each of which is directed at a different molecular target within the allograft response (Figure 1, Table 1). Additive/synergistic effects are achieved through application of each agent at a relatively low dose, thereby limiting the toxicity of each individual agent while increasing the total immunosuppressive effect. Third is the principle that higher immunosuppressive drug doses and/or more individual immunosuppressive drugs are required to gain early engraftment and to treat established rejection than are needed to maintain immunosuppression in the long-term. Hence intensive induction and lower dose maintenance drug protocols are used. Fourth is careful investigation of each episode of post-transplant graft dysfunction, with the realization that most of the common causes of graft dysfunction, including rejection, can (and frequently do) coexist. Successful therapy therefore often involves several simultaneous therapeutic manoeuvres. Fifth, the appropriate reduction or withdrawal of an immunosuppressive drug when that drug’s toxicity exceeds its therapeutic benefit.

Pretransplant transfusions

Although pretransplant random whole blood transfusion was a powerful adjunct to transplant therapy when cyclosporin (CsA) was not available, the short-term benefits of random transfusion have recently been more difficult to demonstrate in the CsA era. There is no agreement concerning the role of donor-specific transfusions (DST) for recipients of HLA mismatched living related donor renal transplants (LDR). Occasionally DST produces adverse presensitization to the donor. Because these sensitized patients cannot be transplanted with tissues procured from the transfusion donor, many units do not employ routine DST. Owing to the powerful tolerizing effects of DST in experimental models, there are several active clinical trials evaluating various forms of pre/peroperative donor blood element infusions into graft recipients as a therapeutic modality.

Therapy designed to prevent rejection

Antirejection protocols are aimed at interrupting several discrete stages in the immune activation pathway leading to allograft rejection [1–3]. When possible, selection is undertaken using HLA matching to minimize histoincompatibility between donor and recipient [4,5]. All post-transplant immunosuppressive protocols use at least two agents, each directed at a discrete site in the T cell activation cascade (Figure 1, Table 1).
Immunopharmacology of allograft rejection

CsA and tacrolimus (FK506)

CsA, a small neutral hydrophobic cyclic peptide of fungal origin, and tacrolimus (FK506), a water-soluble macrolide lactone produced by Streptomyces tsukubensis, block the Ca2+ dependent T cell activation pathway [6–9]. Oral doses of both agents are erratically absorbed. The immunosuppressive effects of CsA and FK506 are dependent upon the formation of a heterodimeric complexes that consist of the native compound (CsA or FK506) and its respective cytoplasmic 'immunophilin' receptor protein, cyclophilin [10] or FK binding protein (FKBP) [11,12]. Both CsA:cyclophilin and FK506:FKBP complexes bind calcineurin, a calcium- and calmodulin-sensitive phosphatase, and inhibit its enzymatic activity (Figure 1; Table 1) [13–15]. CsA/FK506-mediated inhibition of calcineurin's phosphatase activity prevents the dephosphorylation of cytoplasmic NF-AT and thereby impedes subsequent import of this DNA binding protein into
The basic immunosuppressive protocol used in most transplant centers involves the use of multiple drugs, (usually CsA or FK506 + corticosteroids + a purine antagonist) each directed at a discrete site in the T-cell activation cascade (Figure 1, Table 1) and each with distinct side-effects [35]. CsA, FK506, azathioprine, mycophenolate mofetil and corticosteroids are already approved by the FDA while the clinical efficacy of rapamycin (an agent that inhibits the prolif-
corticosteroids act to reduce the intensity of leukocytic infiltration in a rejecting allograft has not been fully elucidated; however, release of numerous cytokines is blocked by high-dose steroids, and T-cell trafficking patterns are altered.

OKT3-treated T cells lose their antigen receptor proteins and become literally blinded to the presence of the allograft; thus, rejection abates. OKT3 is superior to standard high-dose corticosteroid therapy for reversing allograft rejection (90% vs 70% success [40]). More than 90% of first rejections and a high percentage of second rejection episodes respond to OKT3 therapy. Nonetheless, OKT3 is often reserved as treatment for corticosteroid-resistant rejection episodes. As antirejection treatment, OKT3 is given as a daily 5-mg i.v. bolus for 5–10 consecutive days.

While prophylactic administration of OKT3 to patients in the immediate post-transplant period is well tolerated, administration of the first and occasionally second dose of OKT3 to patients treated for ongoing rejection often causes a 'capillary leak' syndrome that can lead to severe ARDS-type pulmonary oedema, hypotension, and/or aseptic meningitis [1,2,44]. This syndrome is caused by the release of lymphokines from the OKT3-targeted activated T cells. Because of these troublesome symptoms as well as additional expense, we reserve OKT3 therapy for steroid-insensitive rejection episodes. Subsequent doses are well tolerated. Approximately 75% of patients develop IgG or IgM anti-idiotypic or antiisotypic antibodies against OKT3.

Anti-lymphocyte antibodies are used in many transplant centres as induction therapy in the immediate post-transplant period [42]. Administration of antilymphocyte globulin (ALG) or OKT3 in conjunction with corticosteroids, azathioprine and greatly reduced doses of CsA/FK506 are applied in the immediate post-transplant period. This protocol establishes an immunosuppressive umbrella that enables initial engraftment without immediate use of high dose CsA/FK506 during the early post-transplant period and enables engraftment without use of high dose CsA/FK506 in the critical early post-transplant days during which time renal grafts are highly sensitive to the nephrotoxic effects of CsA/FK506. The incidence of early rejection episodes is reduced by the prophylactic usage of antilymphocyte antibodies. Any incipient rejection is treated by the use of what we view as essentially antirejection strategies to induce immunosuppression. This protocol is particularly beneficial for long term for patients at high risk for immunological graft failure, e.g. broadly presensitized or retransplant patients [43].

Therapy designed to treat established rejection

Low-dose prednisone, CsA/FK506, and purine antagonist maintenance drug therapy is effective in the prevention of acute cellular rejection; each drug blocks a different facet of T-cell activation. Their proximal sites of activity, however, render low-dose prednisone, CsA/FK506, azathioprine, and mycophenolate mofetil ineffective in blocking the activity of already activated T cells or late-acting elements of the allograft response that no longer require helper T-cell input. Thus, these agents do not readily abrogate established an acute rejection episode or totally prevent chronic rejection. Treatment of established rejection requires the use of agents that act against already fully activated T cells. In contrast, high-dose corticosteroids, polyclonal antilymphocyte antibodies, or OKT3 are often successfully utilized as therapies for the treatment of acute cellular rejection.

Approximately, two-thirds of acute cellular rejection episodes will respond to high dose corticosteroid boluses [1]. Steroid-sensitive rejection episodes are typically characterized by a dense infiltration of T cells in the medullary regions of the graft. We often treat the first rejection episode with 1 g of i.v. methylprednisolone daily for 3 consecutive days. The mechanism by which corticosteroids act to reduce the intensity of leukocytic infiltration in a rejecting allograft has not been fully elucidated; however, release of numerous cytokines is blocked by high-dose steroids, and T-cell trafficking patterns are altered.

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Polyclonal or antilymphocyte antibody preparations are derived from animals immunized with human lymphocytes. The antibodies are directed against both lymphocyte-specific and more broadly expressed antigens. More than 80% of steroid-resistant first rejection episodes will respond to these polyclonal antibodies. Patients are skin tested with 0.1 mg of a 1:1,000 dilution of polyclonal antilymphocyte antibodies prior to administration of the first dose and pretreated with diphenhydramine and steroids. Antilymphocyte antibodies, often at a dosage of 10–15 mg/kg, are administered daily by slow i.v. infusion over 4–8 h for 10–14 days. Adverse reactions include anaphylaxis, haemolysis, thrombocytopenia, neutropenia, dyspnoea, chills, fever, hypotension, chemical phlebitis, pruritus, serum, sickness, and chest, flank, and back pain. Unlike the first-dose complications noted with OKT3, the severity of anaphylactoid side-effects to these polyclonal antilymphocyte preparations can increase with subsequent doses. Frank anaphylaxis can occur at any time during treatment. The use of polyclonal antilymphocyte antibodies has decreased because OKT3 is less toxic and comparably effective in reversing rejection.

We rarely treat a kidney transplant recipient for...
more than three rejection episodes in the early post-
transplant period, because third and fourth rejections
tend to be vasculitic forms that are therapeutically resistant, and the risks to the patient from zealous immunosuppression are unacceptably high by that point. In contrast, patients with cardiac allografts who will die with the cessation of cardiac function are treated more vigorously because complete rejection, in the absence of retransplantation, is fatal.

While current drug protocols are far superior to those employed a decade ago, the situation is far from ideal. Most allografts eventually succumb to chronic rejection. Long-term therapy is mandatory. We anticipate clinical application in the near future of more refined immunosuppressive regimens: new drugs, humanized mAbs, and fusion proteins that target discrete steps in antigen recognition, signal transduction, and effector immunity. We are also optimistic regarding the inducibility of antigen specific tolerance in the clinical setting, but a delivery date cannot yet be guaranteed.

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