Immunosuppressive Therapy Protocols in Kidney Transplantation in Adults

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Abstract

In practical terms, regardless of HLA compatibility level, whenever tissues are transplanted from one person to another it is essential to suppress the immune response of the recipient. A variety of methods are available however, the most frequently used ones have the disadvantage of being immunologicaly non specific. The consequence is a difficult balance between immunosuppression sufficient to prevent the tissue rejection and maintenance of immune system at the level of ability to adequately deal with an infection. The goal, not yet achieved, is to find a way of generating donor specific immunosuppression that leaves the immune machinery otherwise completely intact. The major approaches to immunosuppression are described below.

KEY WORDS: drug, immunosuppression, kidney transplant

Introduction

Along with an increase in the frequency of organ transplantation and acquisition of new organs for transplantation, the interest in chemical immunosuppression has dramatically increased. In the 1950s, the choice of immunosuppressive drugs was limited to azathioprine and steroids and, in the 1960s, polyclonal anti-lymphocyte and thymocyte globulins were added to the list (1). A real breakthrough occurred in 1970s, when the first generation selective immunosuppressant, Cyclo-

sporin (CsA), was introduced. In the 1980s, the main interest shifted towards the application of biological agents, mainly monoclonal Antibodies (MAB), to mention only one of those. Finally, in the early 1990s, a wide range of third generation immunosuppressants with highly specific sites of actions emerged. Most of these are currently in clinical trials (2,3).

Material and Methods

The purpose of this work is to present our results and original protocols used in immunosuppressive therapy and images of rejection in kidney transplantation. Also, we have described and compared the results from other authors from this field worldwide. All medical research described in the submitted paper was conducted in accord with ethical standards that promote respect for human beings and protect their health and rights.

Discussion

IMMUNOSUPPRESSIVE AGENTS IN CURRENT CLINICAL USE

Clinical application of strategies designed to reduce alloimmune responses to transplanted organs continually evolves. Available agents and approaches for immunosuppressive therapy used currently or in the past are classified according to their general mechanism of action (Table 1,2). General clinical approaches are usually divided into four main strategies: termed induction, acute rejection prophylaxis, maintenance immunosuppression and acute rejection therapy (4,5). Although the long-term goal in transplantation continues to be achieving tolerance, that is immunological unresponsiveness to the allograft without the requirement for medication, it remains elusive (6). Accordingly, the clinical approach to anti-rejection therapy has been of pharmacological nature, using powerful immunosuppressive medications at or near the dose at which they exhibit toxic side effects (7). These side effects can be classified into two general categories, those that result from immunosup-

PROLIFERATION SIGNAL INHIBITORS
Sirolimus
Everolimus
NON- SPECIFIC INHIBITORS OF CELL DIVISION / NUCLEOTIDE METABOLISM
Azathioprine
Cyclophosphamide
LYMPHOCYTE SELECTIVE INHIBITORS OF CELL DIVISION / NUCLEOTIDE METABOLISM
Mycophenolate mofetil
Mycophenolic acid
Agents Affecting Antigen Presentation
Corticosteroids
Biologic Agents/ Approaches
Polyclonal anti - lymphocyte antibodies
Anti - lymphocyte globulins
Anti - thymocyte globulins
Campath – 1H
Murine monoclonal anti - lymphocyte antibodies
OKT-3
Humanized monoclonals
Basiliximab (anti-CD25) – Chimerized)
Dacluzimab (anti- CD25 – Humanized)
Plasmapheresis +/- intravenous immunoglobulin
Irradiation (ultraviolet; x- ray)

TABLE 1. Immunosuppressive approaches with potential in clinical practice

DAY	MEDICATION	DOSE
Intraoperative	Methyl-Prednisolone	250 mg (or lesser dose, 4 mg/kg)
1	Prednisone	30 mg every 6 hours (or lesser of 2 mg/kg/d)
2	Prednisone	25 mg every 6 hours (or lesser of 1,5 mg/kg/d)
3	Prednisone	20 mg every 6 hours (or lesser of 1,0 mg/kg/d)
4	Prednisone	15 mg every 6 hours (or lesser of 0,9 mg/kg/d)
5	Prednisone	15 mg every 8 hours (or lesser of 0,7 mg/kg/d)
6	Prednisone	15/10/15mg every 8 hours (or lesser of 0,6 mg/kg/d)
7	Prednisone	15/5/15 mg every 8 hours (or lesser of 0,5 mg/kg/d)
8	Prednisone	15 mg every 12 hours (or lesser of 0,4 mg/kg/d)
10	Prednisone	25 mg daily (or lesser of 0,35 mg/kg/d)
14	Prednisone	20 mg daily (or lesser of 0,3 mg/kg/d)
28	Prednisone	17,5 mg daily (or lesser of 0,25 mg/kg/d)
35	Prednisone	15 mg daily (or lesser of 0,2 mg/kg/d)
45	Prednisone	12,5 mg daily
60	Prednisone	10 mg daily

TABLE 2. The sample of post renal transplant corticosteroid maintenance

pression and those that represent other biological effects that differ from the desired immunosuppressive action. Acute rejection occurs when the overall level of immunosuppression is inadequate (8,9). On the other hand, infections (such as Pneumocystis carinii pneumonia or Cytomegalovirus infection) and malignancy (such as skin cancer, B cell lymphoma, Kaposi's sarcoma) are usually associated with excessive immunosuppression (10,11). Other, non - immunological biological effects of these drugs (toxicities) have, in large part, served as dose limiting factors for these agents, largely because the immunosuppressive effects of most available agents occur at or near the dose where these other undesirable effects are also observed (12,13). Thus, the clinicians must work within a relatively narrow "therapeutic window". The various agents available for clinical use are described below according to their usual use in clinical practice (14).

ACUTE REJECTION PROPHYLAXIS AND MAINTENANCE IMMUNOSUPPRESSION

A variety of immunosuppressive drugs available for use in clinical transplantation permits permutations that make up immunosuppressive protocols. Transplantation centers tend to be loyal to their own protocols, which have often been developed in response to local needs and experience (15). Induction for the purpose of transplant immunosuppression refers to a general strategy designed to provide a more intense regimen during the immediate peri – and post – transplantation period seeking to avert or delay the onset of acute rejection (16). The rationale for this approach was largely based upon observations, that early acute rejection episodes have been associated with deleterious long-term effects on transplanted kidneys, and most allograft failure due to acute and chronic rejection occurs during the initial 3 post

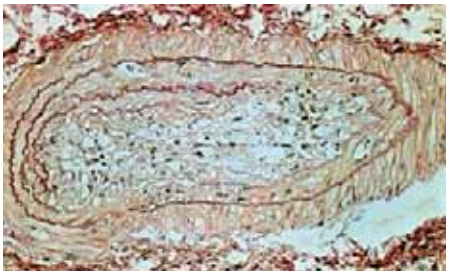

FIGURE 1. Vascular rejection in kidney transplant (Acute rejection).

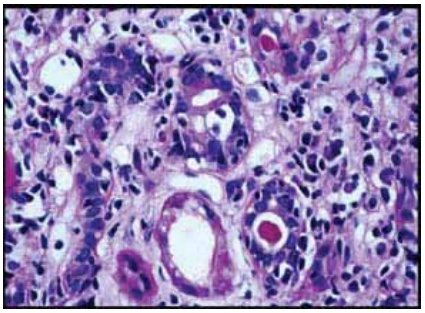

FIGURE 2. Acute tubulitis (Acute rejection).

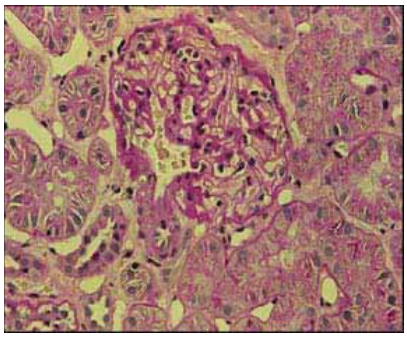

FIGURE 3. Transplant glomerulopathy with slight mesangial matrix increase in transplant nephropathy (Acute rejection).

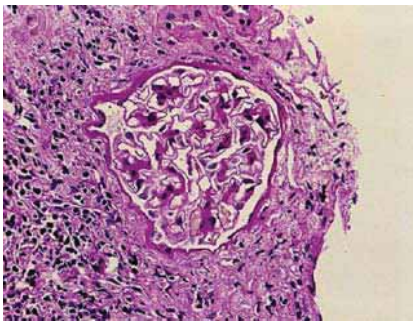

FIGURE 4. Transplant glomerulopathy with no mesangial matrix increase (Acute rejection).

transplant months (Histological appearance of acute and chronic rejection, Figures 1-6). Unfortunately, despite the underlying logic of this approach, it has been difficult to demonstrate clear benefit in clinical practice (17).

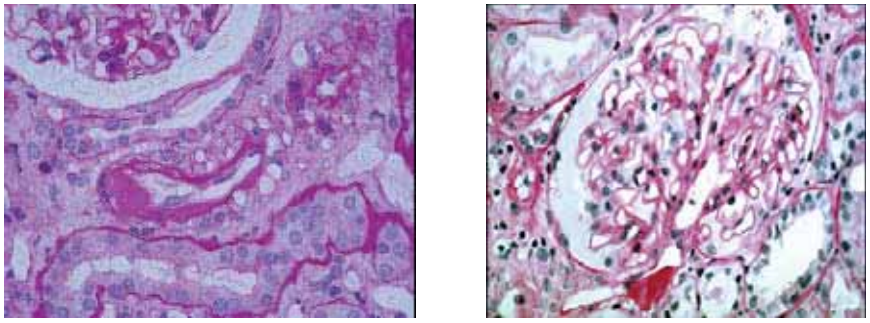

FIGURE 5. and 6. PAS positive nodular hyaline thickening in CsA toxicity in kidney transplant (Chronic rejection)

Conclusion

Renal transplantation has evolved dramatically from an experimental curiosity to mainstream therapy for end stage renal disease during the last 25 years, principally as a result of advances in immunosuppression. Beginning in the 1980s with cyclosporine, then the related calcineurin inhibitor, tacrolimus, the outcome has continued to improve. The selective inhibition of cytokine gene activation exhibited by these agents permitted more effective prophylaxis of acute rejection while sparing major other elements of nonspecific host defense. This has allowed more judicious application of other global agents such as azathioprine, anti-T cell antibody preparations, and more recently mycophenolate mofetil, resulting in overall efficacy and safety. The discovery that sirolimus and more recently everolimus, exert synergistic effects when used in combination with the calcineurin inhibitors, cyclosporine and tacrolimus provided opportunities for the reduction of dose of each agent. One might anticipate this would produce improved efficacy, while minimizing toxicities associated with each agent when given at higher dose. Now, similarly feasible is corticosteroid-free immunosuppression, a particularly important goal due to the substantial co-morbidities associated with long term steroid therapy. Combination therapies that use, for example sirolimus or everolimus with low dose cyclosporine or tacrolimus promise dramatic reduction of the incidence of acute rejection. Alternative approaches using calcineurin inhibitors with mycophenolate mofetil, sirolimus with mycophenolate mofetil may also be beneficial. Together, the available options for post renal transplant immunosuppression will provide increasingly effective, better tolerated approaches, which seem likely to improve the long term outcome for patients after renal transplantation. These approaches will provide the clinicians with increasingly more effective therapies as we eagerly await the future goal of long term allograft tolerance.

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