Transplantation as Treatment of End-Stage Renal Disease

A. MAJOR SIDE EFFECTS OF IMMUNOSUPPRESSIVE AGENTS

<table>
<thead>
<tr>
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<th>Cyclosporine</th>
<th>FK506</th>
<th>Azathioprine</th>
<th>Mycophenolate mofetil</th>
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<tr>
<td>Nephrotoxicity</td>
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<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Neurotoxicity</td>
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</tr>
<tr>
<td>Hirsutism</td>
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<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Gingival hyper trophy</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
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</table>

FIGURE 9-14
The making of a polyclonal antilymphocyte preparation.
Antilymphocyte globulin (ALG) or antithymocyte globulin (ATG) are polyclonal antisera derived from immunization of lymphocytes, lymphoblasts, or thymocytes into rabbits, goats, or horses. These agents have been used prophylactically as induction therapy during the early posttransplantation period and for treatment of acute rejection. Most centers reduce concomitant immunosuppression (eg, stop cyclosporine and lower azathioprine dose) to decrease infectious complications. Antithymocyte gamma globulin (ATGAM) is the only FDA-approved polyclonal preparation. Two rabbit immunoglobulin preparations, raised by immunization with thymocytes or with a human lymphoblastoid line, are scheduled for phase III multicenter testing versus ATGAM or OKT3, respectively. Potential side effects include fever, chills, erythema, thrombocytopenia, local phlebitis, serum sickness, and anaphylaxis. The potential for development of host anti-ALG antibodies has not been a significant problem because of the use of less immunogenic preparations and probably because ALG suppresses the immune response to the foreign protein itself [2,10].

FIGURE 9-13
Side effects of immunosuppressive agents. A. The major side effects of several immunosuppressive agents. The major complication of pulse steroids is increased susceptibility to infection. Other potential problems include acute hyperglycemia, hypertension, peptic ulcer disease, and psychiatric disturbances including euphoria and depression. B. Vasoconstriction of the afferent arteriole (AA) caused by cyclosporine. (From English et al. [22]; with permission.)
OKT3 is a mouse monoclonal antibody directed against the CD3 molecule of the T lymphocyte. OKT3 has been used either from the time of transplantation to prevent rejection or to treat an acute rejection episode. It has been shown in a randomized clinical trial to reverse 95% of primary rejection episodes compared with 75% with high-dose steroids in patients who received azathioprine-prednisone immunosuppression. In patients receiving triple therapy (cyclosporine-azathioprine-prednisone), 82% of primary rejection episodes were successfully reversed by OKT3 versus 63% with high-dose steroids. Like antilymphocyte globulin (ALG), reduction of concomitant immunosuppression (discontinuation of cyclosporine and reduction of azathioprine or mycophenolate mofetil dose) decreases the incidence of infectious complications. Side effects include fever, rigors, diarrhea, myalgia, arthralgia, aseptic meningitis, dyspnea, and wheezing, but these rarely persist beyond the second day of therapy.

Release of tumor necrosis factor (TNF), interleukin-2, and interferon gamma in serum are found after OKT3 injection. The acute pulmonary compromise due to a capillary leak syndrome rarely has been seen because patients are brought to within 3% of dry weight before initiation of OKT3 treatment. Infectious complications, particularly infection with cytomegalovirus, are increased after multiple courses of OKT3.

**A. RECOMMENDED PROTOCOL FOR OKT3 TREATMENT**

- **Evaluation and treatment before administration**
  - Physical examination
  - Laboratory tests including complete blood count
  - Monitor intake and output; record weight changes
  - Chest radiograph
  - Hemodialysis or ultrafiltration for volume overload
- **Premedication on day 0 and 1**
  - Methylprednisolone, 250–500 mg IV given 1 h prior to dose
  - Methylprednisolone or hydrocortisone sodium succinate, 250–500 mg IV given 30 min after the dose
  - Diphenhydramine, 50 mg IV 30 min prior to dose daily
  - Acetaminophen, 650 mg PO 30 min prior to dose
  - Discontinue cyclosporine, maintain azathioprine at 25 mg/d
- **Administer OKT3, 5 mg/d IV, days 0–13**
- **Monitor clinical course**
  - Check CD3 level on day 3
  - Increase OKT3 dosage to 10 mg/d if either:
    - Anti-OKT3 antibody is high
    - OKT3 level is low
    - CD3 level is not low

(Continued on next page)
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**FIGURE 9-16 (Continued)**

B. Monitoring of peripheral blood T cells in a patient receiving OKT3 treatment. The absence of CD3+ cells from the circulation is the best parameter for monitoring the effectiveness of OKT3. Failure of the CD-positive percentage to fall or a fall followed by a rapid rise indicates the appearance of blocking antibodies. Approximately 50% to 60% of patients who receive OKT3 will produce human antimouse antibodies (HAMA), generally in low titers (<1:100). Low antibody titers do not affect the response to retreatment (reversal rate almost 100%) if the rejection episode occurs within 90 days after transplantation. Conversely, titers above 1:100 or recurrent rejection beyond 90 days is associated with a reversal rate of less than 25%. The reversal rate is essentially zero when both high HAMA titers and late rejection are present. PO—orally; IV—intravenous.

**FIGURE 9-17**

New immunosuppressive agents. New agents such as mycophenolate mofetil, FK506, and rapamycin are currently under evaluation for refractory acute rejection. In addition, both mycophenolate and rapamycin prevent chronic allograft rejection in experimental animals. Whether this important observation is reproducible in humans remains to be determined by long-term study.

A, Humanized monoclonal antibodies. The development of genetically engineered humanized monoclonal antibodies will largely eliminate the anti-antibody response, thereby increasing the utility of anti-T-cell antibodies in the treatment of recurrent rejection. Experimental antibody therapies are now being designed to directly target the CD4 molecule, the interleukin-2 receptor, the CD3 molecule by a humanized form of monoclonal anti-CD3, and adhesion molecules such as intercellular adhesion molecule-1 or leukocyte function-associated antigen-1 [23]. Humanized monoclonal antibodies are essentially human immunoglobulin G (IgG), nonimmunologic with a long half-life, and potentially can be administered intravenously about every 2 weeks. Humanized anti-CD25 (IL-2 receptorα chain) monoclonal antibodies has been shown to be effective in lowering the incidence of acute renal allograft rejection. Its role in the treatment of rejection, however, has not been explored. With increasing specificity for lymphocytes, these new agents are likely to have fewer toxicities and better efficacy.

B, Therapeutic application of CTLA41g to transplant rejection. APC—antigen-presenting cell; MHC—major histocompatibility complex; TCR—T-cell receptor.
References