Pharmacology of Immunosuppressive Drugs

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CORE General Surgery RPAC
Site of action of T cell immunosuppressants

1. CD3 Site
2. Ca++
3. Activated calcineurin
4. NFAT-p
5. Gene activation
6. IL-2
7. IL-2 receptor
8. Purines
9. New T Cells

antigen presenting cell

Costimulator Site
CD 28
CD 154

stimulatory lymphokines
IL-3, IL-4, IL-5, IL-6, interferon-γ
<table>
<thead>
<tr>
<th>#</th>
<th>Drug</th>
<th>Mechanism</th>
<th>side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>orthoclone OKT3</td>
<td>monoclonal mouse antibody directed against the CD3 site of the T Cell</td>
<td>first dose effect causing cytokine release syndrome-fever, pulmonary edema, seizures. Can be prevented by pretreatment with glucocorticoid</td>
</tr>
<tr>
<td>2</td>
<td>cyclosporine</td>
<td>binds to cyclophyllin. The cyclosporin-cyclophyllin complex inhibits the activation of nuclear factor of activated T cells (NFAT), which prevents transcription of IL-2. Neoral is a newer formulation which has better bioavailability and is more predictably absorbed.</td>
<td>nephrotoxicity, hepatotoxicity, hypertension, hypercholesterolemia, hirsutism, gum hyperplasia</td>
</tr>
<tr>
<td>3</td>
<td>tacrolimus</td>
<td>binds to nkb-12. The complex then inhibits NFAT activation.</td>
<td>Nephrotoxicity, neurotoxicity, alopecia, diabetes</td>
</tr>
<tr>
<td>4</td>
<td>corticosteroids</td>
<td>binds to cytosolic receptor, migrates to nucleus, binds to glucocorticoid receptor elements on the gene.</td>
<td>Inhibits all immune function, alters metabolism, suppresses adrenal axis, etc.</td>
</tr>
<tr>
<td>5</td>
<td>sirolimus</td>
<td>inhibits activation of rapamycin, a kinase which is required for the binding of IL-2-induced binding factors to the nucleus. Inhibits secretion of a variety of activating factors. Used in conjunction with cyclosporin and glucocorticoids.</td>
<td>decrease WBC, Increase triglycerides</td>
</tr>
<tr>
<td>6</td>
<td>daclizumab</td>
<td>humanized monoclonal antibody directed against the IL-2 receptor on T cells</td>
<td>?</td>
</tr>
<tr>
<td>7</td>
<td>basiliximab</td>
<td>mouse/human monoclonal chimeric antibody directed against the IL-2 receptor.</td>
<td>?</td>
</tr>
<tr>
<td>8</td>
<td>azathioprine</td>
<td>a prodrug mebolized to 6-mercaptopurine. It inhibits de novo synthesis of purines by activated T cells</td>
<td>gi upset, bone marrow depression, rash</td>
</tr>
<tr>
<td>9</td>
<td>mycophenolate mofetil</td>
<td>prodrug converted to mycophenolic acid, which inhibits inosine monophosphate dehydrogenase, a step in the de novo synthesis of purines</td>
<td>gi, bone marrow depression</td>
</tr>
</tbody>
</table>
Reference List


