Optimizing Long-Term Outcomes with Kidney Anti-rejection Therapies
Common Immunosuppressive Regimens: Risks, Benefits and Appropriate Use

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Immunosuppressive Treatment
Strategies for the Transplant Recipient

• Identification of commonly used immunosuppressive drugs
  • Mechanism of action
  • Clinical efficacy
  • Adverse events

• Insights on selecting the most appropriate immunosuppressive regimen for a given patient
Improving Outcomes of Renal Allografts

Year of Transplantation

Acute Rejection
80%

1-Year Graft Survival
45%

90%

Azathioprine
ATG
Radiation
Prednisone
6-Mercaptopurine
CsA
MMF
Tacrolimus
Thymoglobulin
Sirolimus
Everolimus
Daclizumab
Basiliximab
Alemtuzumab
Sirolimus
Everolimus

ATG=antithymocyte globulin; CsA=cyclosporine; MMF=mycophenolate mofetil
1. Alloimmunity follows the same rules as the immune response to other microbes and foreign invaders.

These include:
- The ability to identify self from non-self
- Specificity
- Memory
- Rapid amplification
2. The Cell Cycle of the lymphocyte responds to immunosuppressive drugs like a cancer cell to chemotherapy.

- M:
  - AzA
  - MMF
  - MPA-na

- G2 Late:
  - mTORs
  - Sirolimus
  - Everolimus

- G0:
  - Resting Cell

- G1 Early:

- S:

- M:
  - TMG
  - OKT3
  - C1H

- CNIs
  - CsA
  - Tac
3. Clinical Immunosuppression is a careful balance between too much and not enough.

Too Little
- Rejection
- Recurrent Disease

Too Much
- Infection
- Cancer
Renal Transplantation in Identical Twins in United States and United Kingdom
Nicos Kessaris,1,3 Dayal Mukherjee,2 Pankaj Chandak,2 and Nizam Mamode2

Review of 120 twins in the USA and 12 in the UK between 1988-2004

Graft Survival (%) | 1 yr. | 3 yr. | 5 yr.
--- | --- | --- | ---
99.2 | 91.8 | 88.9
Patient Survival (%) | 100 | 97.1 | 97.1

82 Recipients (68%) were discharged on immunosuppression

<table>
<thead>
<tr>
<th>Immunosuppression</th>
<th>US group Immediately after transplantation</th>
<th>At last follow-up</th>
<th>UK group Immediately after transplantation</th>
<th>At last follow-up</th>
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<tbody>
<tr>
<td>Steroids</td>
<td>70</td>
<td>30</td>
<td>4</td>
<td>3</td>
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<tr>
<td>MMF</td>
<td>45</td>
<td>27</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>FK506</td>
<td>23</td>
<td>17</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>AZA</td>
<td>18</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CYA</td>
<td>30</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>5</td>
<td>7</td>
<td>0</td>
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</tbody>
</table>

MMF, mycophenolate; AZA, asathioprine; CYA, cyclosporine A

Transplantation 2008;86:1572-77.
Clinical Implications for the Principles of Transplant Immunosuppression

1. It is important to prevent a primary immune response; No acute rejection is better than some rejection.
2. It is better to use lower doses of IS drugs that work at different points in the cell cycle than larger doses of a single agent. Impact on tolerability and toxicity.
3. The total amount of IS should be decreased over time as the host accommodates to the foreign HLA phenotypes.
The Fate of Renal Allografts: Immunosuppression

INDUCTION  Treatment of Rejection  MAINTENANCE

<table>
<thead>
<tr>
<th>Scr mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>2</td>
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</tbody>
</table>

Time

Chronic Rejection

Steroids  Anti-lymphocyte Agents
Biologic Targets for Immunosuppressive Agents

Signal 2

Co-stimulation Blockade

Signal 1

Signal 3

Anti-tac

TOR

CD2 CD2

JAK

CD40L (CD154)

CD28

CD4

TCR

OKT3

ZAP-70

SHP

\( \rightarrow \)

\( \rightarrow \)

PLC

Ca\(^{2+} \)

IP3

calmodulin

PKC

Calcineurin

calmodulin complex

\

FKBP

FK506

CyA

cyclosporin

NF-ATp

NF-AT

IL-2

IL-2 receptor

Translation

Aza

MMF

IL-2 gene transcription

Cell cycle

NF-\( \kappa \)B

I\( \kappa \)B\( \alpha \)

I\( \kappa \)B\( \gamma \)

I\( \kappa \)B\( \varepsilon \)

GC

Nucleus

(GC-R)
Immunosuppressive Strategies

1. **Induction Therapy** - high dose therapy
   - prevent a primary immune response
   - decrease passenger leukocytes
   - permit resolution of ischemic renal injury

2. **Maintenance Therapy** - lowest tolerated
   - minimize toxicity
   - rejection prophylaxis

3. **Anti-Rejection Therapy** - high dose therapy
   - limit number of interventions
## Comparative Modes of Action: Induction Antibodies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type of Ab</th>
<th>Target</th>
<th>Principle Adverse Events</th>
<th>Effective Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basiliximab</td>
<td>Chimeric mAb</td>
<td>αChain of the IL2R non T-cell depleting</td>
<td>Mild cytokine release; pneumonitis</td>
<td>2 months</td>
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<tr>
<td>Daclizumab</td>
<td>Humanized mAb</td>
<td>CD3: resting &amp; activated T-cells T-cell depleting</td>
<td>Cytokine release syndrome</td>
<td></td>
</tr>
<tr>
<td>OKT3</td>
<td>Murine mAb</td>
<td>CD3: resting &amp; activated T-cells T-cell depleting</td>
<td>Increased risk of infection and PTLD</td>
<td>1 month</td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td>Rabbit polyclonal Ab</td>
<td>All resting &amp; activated T-cells T-cell depleting*</td>
<td>Increased risk of infection and PTLD</td>
<td>6 months</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Humanized mAb</td>
<td>CD 52: resting &amp; activated T-cells T-cell depleting</td>
<td>Increased risk of infection and PTLD</td>
<td>12 months</td>
</tr>
</tbody>
</table>

*Polyclonal Abs also target surface antigens on B-cells, NK cells, macrophages, neutrophils, and platelets.
Differences in Complementarity-Determining Regions Between IL-2Rα mAb Structures

Chimeric—Basiliximab  Humanized—Daclizumab

Murine variable (V) region: IgG2a, kappa

Human constant region (Fc): IgG1

CDRs=complementarity-determining regions
Trends in the Use of Induction Antibody Therapy in Kidney Transplantation

ATGAM= lymphocyte immune globulin, anti-thymocyte globulin (equine); OKT3= muromonab.

Maintenance Immunosuppression: Multi-drug Therapy with Small Molecules

1. Calcineurin or mTOR Inhibitor:
   • cyclosporine, tacrolimus, sirolimus

2. Anti-proliferative Agents:
   • azathioprine, mycophenolic acid

3. Corticosteroids:
   • low dose, avoidance, withdrawal
**Corticosteroids:** Have numerous effects on the immune system that include sequestration of lymphocytes in lymph nodes and the bone marrow resulting in lymphopenia. Glucocorticoids become bound to intracellular receptors that interfere with cytokine production. Their primary immunosuppressive effect is inhibition of monocyte production and release of interleukin (IL-1), with subsequent inhibition of T cell IL-2 and interferon-gamma; thus interfering with lymphocyte activation and production of effector cells.

The principal adverse reactions include:
- Cushingoid features, hypertension, hyperlipidemia, diabetes
- GI ulcerations, osteoporosis, poor wound healing, cataracts
- Growth retardation, psychiatric disturbances, myopathy, acne

**TDM targets:**
None, 0.05-0.1 mg/kg
Why Steroids at All?

• Anti-inflammatory
• Induce lymphopenia via lympholysis
  – But do enhance lymphatic flow
• Lymphocyte sequestration in RE system
• Demarginate adherent WBC from endothelium
• Enter nucleus and bind to steroid response elements on DNA, resulting in inhibition of transcription of immune regulatory cytokines
  – Inhibit AP-1 and NF-κB
  – Suppression of IL-1 and IL-6 from Monos and Macs
  – Suppression of TNFα and INF-γ from T cells
**Mycophenolate Mofetil**: The 2-morpholinoethyl ester of mycophenolic acid (MPA); potent, selective, non-competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH). MMF inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Since T and B Lymphocytes are critically dependent for their proliferation on the de novo synthesis of purines, and other cell types can utilize salvage pathways, MMF has potent cytostatic effects on lymphocytes.

The principal adverse reactions include:
- GI: nausea, vomiting, diarrhea, colitis
- Marrow suppression: leukopenia, anemia, thrombocytopenia
- Infection: opportunistic, cases of PML
- Pregnancy: should be avoided

TDM targets: $C_0$ 2-4 mg/L
Azathioprine: Competitive inhibitor of purine biosynthesis preventing the proliferation of activated T and B cells, thereby blocking both cellular and humoral immune responses inhibits lymphocyte proliferation in late G2 phase of the cell cycle.

The principal adverse reactions include:
- GI: nausea, vomiting, diarrhea
- Marrow suppression: leukopenia, anemia, thrombocytopenia
- Infection: opportunistic
- Liver toxicity-transaminasemia, alopecia

TDM targets: None, WBC
**Cyclosporine**: A fungal endecapeptide binds to a specific intracellular immunophillin (cyclophilin) with subsequent engaging of the enzyme calcineurin phosphatase; thereby preventing the downstream gene transcription of IL-2 and other cytokines required for T-cell activation and proliferation.

The principal adverse reactions include:
- Marrow suppression: leukopenia, anemia, thrombocytopenia
- Acute and Chronic Nephrotoxicity; hepatotoxicity
- Gingival hyperplasia, hirsutism
- Hypertension, hyperkalemia, hyperuricemia, dyslipidemia

**TDM targets:**
- $C_o \ 100-250 \ \text{ng/mL}$
- $C_2 \ 500-1000 \ \text{ng/mL}$

**Formula:** $C_{62}H_{111}N_{11}O_{12} \ \text{Mol. Wt.:} \ 1202.6$
Tacrolimus: A fungal peptide. Binds to a specific intracellular immunophillin (FKBP12) with subsequent engaging of the enzyme calcineurin phosphatase; thereby preventing the downstream gene transcription of IL-2 and other cytokines required for T-cell activation and proliferation.

The principal adverse reactions include:
- Acute and Chronic Nephrotoxicity; Neurotoxicity, tremors
- Marrow suppression: leukopenia, anemia, thrombocytopenia
- Hyperglycemia and diabetes
- Hyperkalemia, hypomagnesemia

TDM targets:
$C_o \ 6-12 \ \text{ng/mL}$
Sirolimus: A fungal peptide. Similar molecular structure to the calcineurin inhibitors, and binds to the same immunophillin (FKBP-12) as tacrolimus. However, their mode of action appears to be distinct, as the sirolimus complex does not inhibit calcineurin. Instead, the sirolimus-FKBP complex appears to engage a distinct p70 kinase called mTOR (molecular target of rapamycin). The inhibition of mTOR blocks IL-2 signal transduction pathways that prevent cell-cycle progression from G1 to S phase in activated T cells.

The principal adverse reactions include:
- Dyslipidemia, delayed wound healing and lymphoceles
- Marrow suppression: leukopenia, anemia, thrombocytopenia
- Oral ulcer, skin rash-acne, non infectious pneumonitis

TDM targets:
$C_0$ 8-12 ng/mL
Trends in Discharge Immunosuppression Regimens for Kidney transplantation, 1995-2004

## Tailoring Immunosuppression to Limit Potential Side Effects

<table>
<thead>
<tr>
<th>Limiting Side Effects</th>
<th>Depleting Antibodies</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
<th>Sirolimus Everolimus</th>
<th>Steroids</th>
<th>MMF</th>
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<tr>
<td>NODAT</td>
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<td>Dyslipidemia</td>
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<td>Wound Healing</td>
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<td>Solid/Skin Cancers</td>
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<td>↓↓</td>
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Immunosuppressive Treatment Strategies for the Transplant Recipient

- Immunosuppressive Therapy is necessary to prevent the rejection of organ allografts
- Organ allografts are subject to the same rules that govern the immune response to microbes and other foreign invaders
- Induction therapy using antibodies are more frequently used today to prevent a primary immune response
- Multidrug maintenance regimens are most often used to maximize efficacy and minimize individual drug toxicity
- Tailoring immunosuppression is possible to further control side effects in higher risk recipients