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Immunosuppression in kidney transplantation

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Immunosuppression

- Prevention of rejection.
- Ideal immunosuppression:

  selective, adjusted to immune response.
- Gradual decrease of immune response after Tx.
- Reduction of immunosuppression from its highest level in early period to maintenance long-term therapy.

Immunosuppression

- **Increase of imm.: infections, malignancies, specific side effects.**
- **Decrease of imm.: rejection.**

Calcineurin inhibitors

- Cyclosporine (e.g. Sandimmun Neoral)
- Tacrolimus (Prograf, Advagraf)
- **Mechanism**: inhibition of IL-2 production →

  → inhibition of T lymphocyte proliferation.
- **Backbone** of preventive immunosuppression.

Characteristics of calcineurin inhibitors

	Cyclosporine	Tacrolimus
Ch. structure	polypeptide	macrolide
Route of administration	o., iv.	o., iv.
Effectiveness	+	++
Interactions	similar	similar

Side effects of calcineurin inhibitors

	Cyclosporine	Tacrolimus
Nephrotoxiticy	+	+
Cosmetic	++	+
Hypertension	++	+
Hypercholesterolemia	++	+
Glucose intolerance	+	++
Neurotoxiticy	+	++
Gastrointestinal	+	++

Drugs that increase C.I. blood levels

- **Calcium-channel blockers (diltiazem, verapamil, amlodipine, nicardipine),**
- **Antifungal agents (ketoconazole, fluconazole, itraconazole, voriconazole),**
- **Antibiotics (erythromycin, clarithromycin),**
- **Grapefruit juice.**

Drugs that decrease C.I. blood levels

- **Antibiotics (rifampin),**
- **Anticonvulsants (barbiturates, phenytoin, carbamazepine),**
- **St. John's wort (antidepressant herbal preparation).**

Calcineurin inhibitors and statins

- **Statins + cyclosporine → rhabdomyolysis.**
- **Rosuvastatin; max. 10 mg/day.**
- **Lovastatin, simvastatin; max. 20 mg/day.**
- **Atorvastatin; max. 20 mg/day.**
- **Pravastatin; max. 40 mg/day.**
- **Fluvastatin; max. 80 mg/day.**

Mycophenolate mofetil (MMF, CellCept)

- **Synthetic ester of mycophenolic acid (MPA).**
- **Prevention of rejection.**
- **Main adjunctive immunosuppressive drug.**
- **MMF is more effective than azathioprine (reduction in incidence of acute rejections from app. 40% to 20%).**

Mycophenolate mofetil (MMF)

- **MMF inhibits IMPDH → blocks 'de novo' synthesis of guanosine nucleotides in T and B ly.**
- **MMF inhibits proliferation of T and B ly., antibody formation.**
- **Relatively selective effect on lymphocytes.**

Side effects of MMF

- **Gastrointestinal: diarrhea, abdominal pain, nausea, vomiting, esophagitis, gastroenteritis, GI hemorrhage.**
- **Leukopenia, anemia, thrombocytopenia.**
- **MMF should be discontinued before pregnancy!**

MMF - drug interactions

- **MMF + azathioprine → ↑ hematologic toxicity (should not be administered concomitantly!),**
- **MMF + tacrolimus → ↑ concentration of MPA (adjustment of MMF dose),**
- **MMF + allopurinol can be administered without dose adjustment.**

Mycophenolate sodium (Myfortic)

- **Pharmacodynamic proprerties equal to that of MMF.**
- **Clinical efficacy comparable to MMF.**
- **Myfortic 360 mg = CellCept 500 mg.**
- **GI side effects not significantly different from MMF.**
- **Could be administered simultaneously with PPI.**

Sirolimus (rapamycin, Rapamune)

- **Macrolide antibiotic**
- **Prevention of rejection.**
- **Adjunctive immunosuppressive drug.**
- **More effective than azathioprine.**

Sirolimus (S.)

- **S. blocks TOR ($G_1 \rightarrow$ | S phase of cell-division cycle) and proliferative response of cells to IL-2.**
- **S. inhibits proliferation of T and B lymphocytes, synthesis of Ig.**
- **S. inhibits proliferation of arterial smooth muscle cells (chronic rejection).**

Sirolimus - drug interactions

Drugs that increase S. blood levels:

- **Cyclosporine,**
- **Calcium-channel blockers (diltiazem),**
- **Antifungal agents (ketoconazole).**

Drugs that decrease S. blood levels:

- **Antibiotics (rifampin),**
- **Anticonvulsants (barbiturates, carbamazepine, phenytoin).**

Side effects of Sirolimus

- **Nephrotoxicity with standard doses of c. i.,**
- **“De novo” proteinuria, limb edema, angioedema,**
- **Hypercholesterolemia, hypertrigliceridemia,**
- **Wound healing impairment, lymphoceles, mouth ulcers,**
- **Thrombocytopenia, leukopenia, anemia,**
- **Oligospermia, pneumonia.**

Sirolimus

- It probably has antineoplastic potential (Kaposi s., skin c.,.....?); Monaco AP. Transplantation 2009; 87: 157.
- Appropriate in pts. at high risk for post-transplant. mlg.,
- For pts. who develop *de novo* mlg. after transplantation.

Everolimus (Certican)

- Pharmacodynamic properties equal to that of sirolimus ("TOR inhibitor").
- Shorter half-life.
- Similar side effects.
- It allows calcineurin inhibitor reduction without loss of efficacy. (Tedesco Silva H Jr et al. Am J Transplant 2010; 10: 1401.)

Azathioprine (Imuran)

- **Thiopurine**
- **Prevention of rejection (since 1961).**
- **Adjunctive immunosuppressive drug.**
- **Azathioprine → 6-mercaptopurine →**

  6-thioinosinic acid.

Azathioprine

- **A. inhibits synthesis of purine nucleotides, DNA and RNA,**

- **A. inhibits proliferation of lymphocytes.**

Side effects of Azathioprine

- **Bone marrow suppression: leukopenia, thrombocytopenia, anemia,**
- **Hepatitis,**
- **Alopecia,**
- **Pancreatitis.**

Azathioprine - drug interactions

- **Azathioprine + allopurinol (xanthine oxidase inhibitor) $\rightarrow \uparrow$ immunosuppression and side effects (hematologic toxicity).**
- **25% of initial dose + allopurinol!**

Glucocorticoids

- **Prednisone, Prednisolone, Methylprednisolone**
- **Treatment of a. rejection (high doses, since 1960).**
- **Prevention of rejection (low doses, since 1962).**

Glucocorticoids

- **Specific actions on macrophages and T cells;**

  inhibit production of IL-1, -2, -3, -6, TNF-α, IFN-γ.

- **Nonspecific immunosuppressive and**

  antiinflammatory effects.

Side effects of glucocorticoids

- **Hypertension, glucose intolerance, hyperlipidemia, osteoporosis, osteonecrosis, muscle weakness.**

- **Growth impairment, impaired wound healing and resistance to infection, obesity, Cushingoid habitus, skin thinning and bruising, acne, cataract, psychiatric and gastrointestinal disturbances.**

Steroid withdrawal / avoidance

- **Within the first week**; KDIGO.... Am J Transplant 2009; 9 (Suppl 3): S10.
- **After 3 to 6 months**; Pascual J et al. Transplantation 2010; 90: 343.
- **No earlier than 6 months**; Opelz G et al. Am J Transplant 2005; 5: 720.

- **Steroid avoidance**; Cantarovich D et al. Transpl Int 2010; 23: 313.

Polyclonal antibodies

- **Antithymocyte globulin (ATG);**

  Atgam (immunization of horses),

  Thymoglobulin and

  ATG Fresenius (immunization of rabbits).

- **Induction immunosuppression.**
- **Treatment of acute rejection.**

Polyclonal antibodies

Lymphopenia:

opsonization of T ly. (RES),

lysis of T ly. (complement activation).

Monoclonal antibodies

- **Muromonab-CD3 (Orthoclone OKT3) - murine a.**
- **Basiliximab (Simulect) - chimeric antibody.**
- **Daclizumab (Zenapax) - humanized antibody.**
- **Rituximab (MabThera) - chimeric antibody.**
- **Alemtuzumab (MabCampath) - humanized a.**

OKT3

- **Induction immunosuppression**
- **Treatment of acute rejection.**
- **Anti-CD3 → deactivation of CD3 →**

  → endocytosis of TCR →

  → T ly. become ineffectual→ RES.

Side effects of OKT3

- **Cytokine release syndrome:**

  chills, fever, noncardiogenic pulmonary edema,

  nephrotoxicity,

- **Neurologic complications (aseptic meningitis),**
- **Rejection recurrence, allograft thrombosis, TMA,**

  infection (CMV), malignancy (lymphoma).

- **Use of OKT3 administration protocol!**

Basiliximab (Simulect) and Daclizumab *(Zenapax)

- **Induction immunosuppression**
- **Binding to alpha chain (CD25) of IL-2R on activated T lymphocytes.**
- **Prevention of IL-2 binding and proliferation of activated T lymphocytes.**

* Zenapax production was discontinued in 2009.

Basiliximab (Simulect) and Daclizumab (Zenapax)

- **Basiliximab (chimeric) and Daclizumab (humanized) reduce incidence of acute rejections in combination with cyclosporine and steroids.**

- **Absence of significant side effects.**

Rituximab (MabThera)

- **Directed against CD20 antigen on B lymphocytes.**
- **Rapid and sustained depletion of circulating and tissue-based B cells.**
- **Treatment of acute humoral rejection.**

Alemtuzumab (MabCampath)

- **Directed against CD52 antigen on B and T lymphocytes.**
- **Rapid and sustained depletion of lymphocytes.**
- **Induction immunosuppression.**
- **Minimization of maintenance immunosuppression without steroids?**

Immunosuppressive protocol drugs

(Renal Transplant Center of University Medical Center Ljubljana, 2011)

- **Basiliximab**
- **Cyclosporine**
- **Mycophenolate mofetil**
- **Methylprednisolone**

Diltiazem, antimicrobial prophylaxis (amoxicillin/clavulanate, miconazole,

TMP-SMX, valganciclovir, isoniazid, lamivudine)

Immunosuppressive protocol (1)

(Renal Transplant Center of University Medical Center Ljubljana, 2011)

(1) Basiliximab (Simulect, Novartis): 20 mg infusion on day 0 and on day 4.

(2) CyA (Novartis): continuous infusion (0.08mg/kg/h) started at operation, replaced by CyA-Neoral (3mg/kg b.i.d.) on day 2.

Immunosuppressive protocol (2)

(Renal Transplant Center of University Medical Center Ljubljana, 2011)

(3) Mycophenolate mofetil (CellCept, Roche): 750 mg t.i.d. orally (500mg t.i.d. in patients with b.w. < 50kg) started on day 1.

(4) Methylprednisolone: 0.4mg/kg iv. at operation, and from day 1 through day 3.

Immunosuppressive protocol (3)

(Renal Transplant Center of University Medical Center Ljubljana, 2011)

- **CyA-Neoral dose adjustment to maintain blood trough levels of 100 - 170 ng/ml in first 3 months, and 70 - 130 ng/ml (EIA) thereafter.**

- **Oral methylprednisolone started on day 4 at 0.4 mg/kg/day and tapered by 4mg per week to achieve maintenance dose of 0.08mg/kg/day.**