GLUCOCORTICOIDs
Fig. 1. Asse ipotalamo-ipofisi-surrene. Stimoli stressogeni, mediatori lipidici, citochine stimolano a livello ipotalamico la produzione di CRH, che stimola la adenoipofisi a produrre ACTH, che, a sua volta, induce un aumento della sintesi di ormoni corticosurrenalici. I glicocorticoidi inibiscono con vari meccanismi a livello sia ipotalamico che ipofisario la sintesi e l’attività biologica di CRH ed ACTH ed inoltre bloccano la sintesi di mediatori e citochine. Con tale meccanismo a feedback negativo i glicocorticoidi sono in grado di controllare l’attivazione dell’asse ipotalamo-ipofisi-surrene e quindi la propria sintesi.

Mineralocorticoidi (Glomerulosa)
Glucocorticoidi (Fasciculata)
Glucocorticoids Synthesis Inhibitors

- Metyrapone
- Aminoglutethimide
- Ketoconazole
- Mitotane
- Trilostane

Receptor Antagonists

- Mifepristone (RU 486)

Increase in Glucocorticoids

Cushing Syndrome

Asthenia and easy fatigability due to increased protein, bone and skin catabolism; osteoporosis, weight gain with obesity, particularly at the trunk and face level; loss of libido, impotence, frigidity; hypertension; amenorrhea, dysmenorrhea and hirsutism in women; hyperglycemia, type II diabetes mellitus and glucose intolerance; psychological problems (depression, psychosis, nervousness and irritability); skin problems with areas of atrophy and reddish-purple streaks typical on the hips on the abdomen and lower limbs, seborrhea; bone and joint pains; lengthening of the healing time and tendency to infections (decrease in lymphocytes)
Glucocorticoids

Metabolic actions
- **Carbohydrates:** decreased uptake and utilisation of glucose accompanied by increased gluconeogenesis; this causes a tendency to hyperglycaemia.
- **Proteins:** increased catabolism, reduced anabolism.
- **Lipids:** a permissive effect on lipolytic hormones and a redistribution of fat, as observed in Cushing’s syndrome.

Regulatory actions
- **Hypothalamus and anterior pituitary gland:** a negative feedback action resulting in reduced release of endogenous glucocorticoids.
- **Cardiovascular system:** reduced vasodilatation, decreased fluid exudation.
- **Musculoskeletal:** decreasing osteoblast and increasing osteoclast activity.

*Inflammation and immunity:*
  - **acute inflammation:** decreased influx and activity of leucocytes
  - **chronic inflammation:** decreased activity of mononuclear cells, decreased angiogenesis, less fibrosis
  - **lymphoid tissues:** decreased clonal expansion of T and B cells, and decreased action of cytokine-secreting T cells.

- **Mediators:**
  - decreased production and action of cytokines, including interleukins, tumour necrosis factor-α and granulocyte macrophage colony-stimulating factor
  - reduced generation of eicosanoids
  - decreased generation of IgG
  - decrease in complement components in the blood
  - increased release of anti-inflammatory factors such as interleukin-10 and annexin 1.

- **Overall effects:** reduction in the activity of the innate and acquired immune systems, but also decreased healing and diminution in the protective aspects of the inflammatory response.
Mechanism of action of glucocorticoids

Coactivators:
SRC (steroid), GRIP (glucocorticoid), CBP (cAMP)
### Tabella 47.3. Meccanismo antinfiammatorio ed immunosoppressore dei glucocorticoidi.

<table>
<thead>
<tr>
<th>Inibizione della sintesi di proteine proinfiammatorie ed immunostimolanti</th>
<th>Induzione della sintesi di proteine antinfiammatorie ed immunodepressive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Citochine e recettori</strong></td>
<td>Annessina-1 ♠</td>
</tr>
<tr>
<td>IL-1, [IL-2, IL-3, IL-4, IL-5] IL-6, IL-12</td>
<td>Recettore di tipo II per IL-1</td>
</tr>
<tr>
<td>TNFα, IFNγ</td>
<td>IkBα</td>
</tr>
<tr>
<td>Recettori per IL-2</td>
<td>GILZ</td>
</tr>
<tr>
<td>Chemochine</td>
<td>MAPK fosfatasi-1</td>
</tr>
<tr>
<td>IL-8</td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td></td>
</tr>
<tr>
<td><strong>Fattori di crescita</strong></td>
<td></td>
</tr>
<tr>
<td>GM-CSF</td>
<td></td>
</tr>
<tr>
<td>G-CSF</td>
<td></td>
</tr>
<tr>
<td><strong>Molecole di adesione</strong></td>
<td></td>
</tr>
<tr>
<td>E-selectin</td>
<td></td>
</tr>
<tr>
<td>ELAM-1</td>
<td></td>
</tr>
<tr>
<td>ICAM-1</td>
<td></td>
</tr>
<tr>
<td><strong>Enzimi</strong></td>
<td>Activate immune system</td>
</tr>
<tr>
<td>Fosfolipasi A₂</td>
<td></td>
</tr>
<tr>
<td>Cicloossigenasi inducibile</td>
<td>Inflammatory response</td>
</tr>
<tr>
<td>Nitrossidosintasi inducibile</td>
<td></td>
</tr>
<tr>
<td>Collagenasi</td>
<td></td>
</tr>
<tr>
<td>Collagenasi</td>
<td></td>
</tr>
<tr>
<td>Metalloproteinasin</td>
<td></td>
</tr>
</tbody>
</table>

• Glucocorticoids bind intracellular receptors that then dimerise, migrate to the nucleus, and interact with DNA to modify gene transcription, inducing synthesis of some proteins and inhibiting synthesis of others.

• *Metabolic actions*: most mediator proteins are enzymes, for example cAMP-dependent kinase, but not all actions on genes are known.

• *Anti-inflammatory and immunosuppressive actions*: known actions include:
  — inhibition of transcription of the genes for cyclooxygenase-2, cytokines and interleukins, cell adhesion molecules, and the inducible form of nitric oxide synthase
  — block of vitamin D₃-mediated induction of the osteocalcin gene in osteoblasts, and modification of transcription of the collagenase genes
  — increased synthesis and release of annexin-1, which has potent anti-inflammatory effects on cells and mediator release, and may also mediate negative feedback at the level of the hypothalamus and anterior pituitary gland.

• Some rapid non-genomic effects of glucocorticoids have also been observed.
Fig. 1. Asse ipotalamo-ipofisi-surrenale. Stimoli stressogeni, mediatori lipidici, citochine stimolano a livello ipotalamico la produzione di CRH, che stimola la adenoipofisi a produrre ACTH, che, a sua volta, induce un aumento della sintesi di ormoni corticosurrenali. I glicocorticoidi inibiscono con vari meccanismi a livello sia ipotalamico che ipofisario la sintesi e l’attività biologica di CRH ed ACTH ed inoltre bloccano la sintesi di mediatori e citochine. Con tale meccanismo a feedback negativo i glicocorticoidi sono in grado di controllare l’attivazione dell’asse ipotalamo-ipofisi-surrenale e quindi la propria sintesi.
Mineralocorticoid Activity

Renin-angiotensin-aldosterone system

[Diagram showing the mineralocorticoid activity process]

- Angiotensinogen → Angiotensin I → Angiotensin II
- Surface of pulmonary and renal endothelium: ACE
- Liver
- Kidney
- Lungs
- Sympathetic activity
- Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion, H₂O retention
- Adrenal gland: cortex
- Aldosterone secretion
- Arteriolar vasoconstriction, Increase in blood pressure
- ADH secretion
- Pituitary gland: posterior lobe
- Collecting duct: H₂O absorption
- Na⁺ K⁺ Cl⁻ H₂O
- Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
CORTICOSTEROID DRUGS
<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative affinity for glucocorticoid receptors&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Approximate relative potency in clinical use</th>
<th>Duration of action after oral dose&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone (cortisol)</td>
<td>1</td>
<td>Anti-inflammatory 1 Sodium retaining 1</td>
<td>Short</td>
<td>Drug of choice for replacement therapy</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.01</td>
<td>0.8</td>
<td>0.8</td>
<td>Cheap; inactive until converted to hydrocortisone; not used as anti-inflammatory because of mineralocorticoid effects</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>0.85</td>
<td>0.3</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Prednisolone ✯</td>
<td>2.2</td>
<td>4</td>
<td>0.8</td>
<td>Drug of choice for systemic anti-inflammatory and immunosuppressive effects</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.05</td>
<td>4</td>
<td>0.8</td>
<td>Inactive until converted to prednisolone</td>
</tr>
<tr>
<td>Methylprednisolone✯11.9</td>
<td>5</td>
<td>Minimal</td>
<td>Intermediate</td>
<td>Anti-inflammatory and immunosuppressive</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>1.9</td>
<td>5</td>
<td>None</td>
<td>Relatively more toxic than others</td>
</tr>
<tr>
<td>Dexamethasone ✯</td>
<td>7.1</td>
<td>30</td>
<td>Minimal</td>
<td>Anti-inflammatory and immunosuppressive, used especially where water retention is undesirable (e.g. cerebral oedema); drug of choice for suppression of adrenocorticotrophic hormone production</td>
</tr>
<tr>
<td>Betamethasone ✯</td>
<td>5.4</td>
<td>30</td>
<td>Negligible</td>
<td>Anti-inflammatory and immunosuppressive, used especially when water retention is undesirable</td>
</tr>
<tr>
<td>Deoxycortone</td>
<td>0.19</td>
<td>Negligible</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>3.5</td>
<td>15</td>
<td>150</td>
<td>Drug of choice for mineralocorticoid effects</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>0.38</td>
<td>None</td>
<td>500</td>
<td>Endogenous mineralocorticoid</td>
</tr>
</tbody>
</table>
Glucocorticoidi

<table>
<thead>
<tr>
<th>Steroido</th>
<th>Effetto antiinfiammatorio</th>
<th>Effetto di ritenzione salina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idrocortisone</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0,8</td>
<td>0,8</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0,3</td>
<td>4</td>
</tr>
<tr>
<td>Prednisoione</td>
<td>0,8</td>
<td>5</td>
</tr>
<tr>
<td>Metilprednisolone</td>
<td>0,5</td>
<td>5</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Betametasone</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Desametasone</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Parametasone</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Desossicorticosterone</td>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>

Mineralcorticoidi
Replacement therapy for patients with adrenal failure (*Addison’s disease*).

Anti-inflammatory/immunosuppressive therapy

- **in asthma**
- topically in various inflammatory conditions of skin, eye, ear or nose (e.g. eczema, *allergic conjunctivitis* or *rhinitis*)
- **hypersensitivity states** (e.g. severe allergic reactions)
- in miscellaneous diseases with autoimmune and inflammatory components (e.g. *rheumatoid arthritis* and other ‘connective tissue’ diseases, *inflammatory bowel diseases*, some forms of *haemolytic anaemia*, *idiopathic thrombocytopenic purpura*)
- to prevent **graft-versus-host disease** following organ or bone marrow transplantation.

In **neoplastic disease**

- in combination with cytotoxic drugs in treatment of specific malignancies (e.g. *Hodgkin’s disease*, *acute lymphocytic leukaemia*)
- to reduce cerebral oedema in patients with metastatic or primary brain tumours (**dexamethasone**)
Endocrinological indications

• Adrenocortical insufficiency (Addison’s disease)
• Secondary adrenocortical insufficiency (panhypopituitarism)
• Androgenital syndrome
Rheumatological indications
(prednisolone, methotrexate)

• Systemic lupus erythematosus (SLE) *
• Polymyositis and Dermatomyositis *
• Vasculitis *
• Polymyalgia and rheumatic fever *
• Rheumatoid arthritis
• Sjogren's syndrome

* first choice drugs
Pneumological indications
(methylprednisolone, prednisolone)

- State of asthmatic disease
- Sarcoidosis (in active phase)
- Bronchial asthma (by inhalation)
- Interstitial pulmonary fibrosis (in active phase)
Nephrological indications (prednisolone)

- Minimal change glomerulonephritis with nephrotic syndrome
- Secondary glomerulonephritis (SLE, cryoglobulinemia)
- Rapidly progressing glomerulonephritis
- Membranous glomerulonephritis with nephrotic syndrome
- Local sclerosing glomerulonephritis with nephrotic syndrome
Dermatological indications

- Pemphigus *
- Bullous pemphigoid *
- Erythroderma *
- Eczema
- Acute urticaria
- Angioedema
- Erythema multiforme
- Atopic dermatitis
- Chronic lichen simplex
- Toxic epidermal necrolysis

* administered systemically only in severe episodes
Gastrointestinal and hepatic indications (hydrocortisone, prednisone)

- Ulcerative colitis (in active phase)
- Crohn's disease (in active phase)
- Chronic active hepatitis
- Cholestatic viral hepatitis
Haematological indications

- Acute leukemias
- Hodgkin's and non-Hodgkin's lymphomas
- Autoimmune hemolytic anemias
- Idiopathic purpura
- Thrombocytopenia
- Multiple myeloma
- Aplastic anemia
- Agranulocytosis
Infectious indications *

• Septicemia from gram-negative bacteria with excessive inflammatory response
• Haemophilus influenzae meningitis
• Viral meningoencephalitis
• Pneumocystis carinii pneumonia
• Infectious mononucleosis
• Tuberculosis with exudative component

*In bacterial infections, treatment should be combined with antibiotics
Pharmacokinetics and unwanted actions of the glucocorticoids

- Administration can be oral, topical or parenteral. The drugs are transported in the blood by corticosteroid-binding globulin and enter cells by diffusion. They are metabolised in the liver.
- Unwanted effects are seen mainly after prolonged systemic use as anti-inflammatory or immunosuppressive agents but not usually with replacement therapy. The most important are:
  - suppression of response to infection
  - suppression of endogenous glucocorticoid synthesis
  - metabolic actions
  - osteoporosis
  - iatrogenic Cushing’s syndrome
Corticosteroids: therapeutic utilization

Risk-benefit
Dosage-Duration of therapy suspension

Metabolism alteration:
- increased gluconeogenesis + glucose in the blood (diabetes)
- lipolysis (free fat increase)

- organic defenses; Immune system
- tissue repair processes
- lymphocytes, eosinophils, monocytes, basophils (polymorphonuclear leukocytes ↑)
- renal function HPA (suspension)
- suspension syndrome: (arthralgia, myalgia, fever)
Side Effects
Therapeutic Effects

- Immunosuppression
- Antiinflammatory
- Anti-allergy
- Pain relief (secondary)

Immune cells, tissues & organs

Blood Vessels
- Blood vessel permeability

CV/Renal
- Hypertension
- Cataracts Glaucoma

Muscle
- Myopathies
- Osteoporosis
- Aseptic necrosis of femur

Bone
- Skin
- Metabolic

Skin thinning
- Hyperglycemia
- Weight gain
- Fluid retention
- Cushingoid appearance

CNS Adrenal
- HPA insufficiency
- Neuropsychiatric disorders
Decalogue for the administration of glucocorticoids

1) To be utilized only after a definite diagnosis
2) The therapeutic dose has to be defined step by step
3) Administration of drugs should be at the lowest effective dose for the shortest time. Best time of the day 8:00 am
4) Administration should be every other day as soon as possible
5) Reduce intake of food to prevent gain in weight
6) Reduce Na intake to prevent edema. If necessary increase intake of K
7) When possible, integrate NSAID and reduce glucocorticoid dose
8) Severity of side effects increases with dose and time of administration
9) Avoid sudden interruptions
10) Administration of high dose for only 1 week causes negligible side effects
IMMUNOSUPPRESSANTS
• Immunosuppressants are used for three main purposes:
  — to suppress rejection of transplanted organs and tissues (kidneys, bone marrow, heart, liver, etc.)
  — to suppress graft-versus-host disease (i.e. the response of lymphocytes in the graft to host antigens) in bone marrow transplants
  — to treat a variety of conditions that, while not completely understood, are believed to have an important autoimmune component in their pathogenesis: idiopathic thrombocytopenic purpura, some forms of haemolytic anaemia, some forms of glomerulonephritis, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, psoriasis and ulcerative colitis.

• Therapy for this third category often involves a combination of glucocorticoid and cytotoxic agents.

• For transplantation of organs or bone marrow, cyclosporin is usually combined with a glucocorticoid, a cytotoxic drug or an antilymphocyte immunoglobulin.
**Immunosuppressants**

- **Clonal proliferation** of Th cells can be decreased through inhibition of transcription of interleukin-2: ciclosporin, tacrolimus and glucocorticoids act in this way.
  — ciclosporin and tacrolimus are given orally or i.v.; common adverse effect is nephrotoxicity.

- **DNA synthesis** is inhibited by:
  — azathioprine through its active metabolite mercaptopurine
  — mycophenolate mofetil through inhibition of de novo purine synthesis.

- **T cell signal transduction** events are blocked by basiliximab and daclizumab, which are monoclonal antibodies against the α-chain of the interleukin-2 receptor.
# Immunosuppressant drugs

<table>
<thead>
<tr>
<th>Agente farmacologico</th>
<th>Bersaglio metabolico</th>
<th>Effetto principale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclofosfamide</td>
<td>Alchilazione del DNA</td>
<td>Blocco della sintesi del DNA</td>
</tr>
<tr>
<td>Metotressato</td>
<td>Diidrofolato reduttasi</td>
<td>»</td>
</tr>
<tr>
<td>Azatioprina</td>
<td>Sintesi della purine</td>
<td>»</td>
</tr>
<tr>
<td>Micofenolato mofetile</td>
<td>Deidrogenasi IMP</td>
<td>»</td>
</tr>
<tr>
<td>Brequinar</td>
<td>Deidrogenasi diidrorato</td>
<td>»</td>
</tr>
<tr>
<td>15-Desossispergualina</td>
<td>Sconosciuto</td>
<td>Immunosoppressione</td>
</tr>
<tr>
<td>Corticosteroidi</td>
<td>Recettore per gli steroidi</td>
<td>Inibizione della sintesi di citochine</td>
</tr>
<tr>
<td>Anticorpi monoclonali anti-TCR, OKT3</td>
<td>ComplessO TCR/CD3</td>
<td>Blocco dell’attivazione dei linfociti ed deplezione linfocitaria</td>
</tr>
<tr>
<td>Anticorpi monoclonali anti-CD4</td>
<td>CD4</td>
<td>»</td>
</tr>
<tr>
<td>Anticorpi monoclonali anti-IL-2</td>
<td>Recettore per la IL-2</td>
<td>Blocco della attivazione dei linfociti ed effetto antiinflammatorio</td>
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<tr>
<td>Ciclosporina A</td>
<td>Calcineurina</td>
<td>»</td>
</tr>
<tr>
<td>FK-506 (tacrolimus)</td>
<td>Calcineurina</td>
<td>»</td>
</tr>
<tr>
<td>Rapamicina</td>
<td>p70S6k, p33cdk2 e p34cdc2</td>
<td>»</td>
</tr>
<tr>
<td>IL-10</td>
<td>Produzione delle citochine</td>
<td>»</td>
</tr>
</tbody>
</table>

* Basilimax, daclizumab = antibody IL2
## Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Glucocorticoidi</th>
<th>Ciclosporina A</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
<th>Azatioprina</th>
<th>Acido Micofenolico</th>
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</thead>
<tbody>
<tr>
<td>Potenza</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Nefrotossicità</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Neurotossicità</td>
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<td>+</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Irsutismo</td>
<td>++</td>
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<td>-</td>
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<tr>
<td>Rash cutaneo</td>
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<td>+</td>
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<td>+</td>
<td>++</td>
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<td>++</td>
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<td>+</td>
<td>+</td>
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</table>
Fig. 9.4. Meccanismi immunologici fondamentali della risposta antigenica all’allotrasplantato e possibili siti di intervento farmacologico. Gli immunosoppressori aspecifici come i corticosteroidi interferiscono con la sintesi di IL-1 da parte dei macrofagi che presentano l'antigene ai T linfociti; inoltre i corticosteroidi inibiscono la proliferazione dei B e dei T linfociti. Altri immunosoppressori aspecifici (ciclofosfamide, azatioprina e metotrexato) inibiscono la proliferazione e la differenziazione dei B e T linfociti. Viceversa, gli immunosoppressori specifici come la CsA ed il composto FK-506 interferiscono con i meccanismi molecolari che controllano a livello del DNA la sintesi di citochine (IL-2, IL-6, ecc.) che inducono la proliferazione dei T linfociti helper. Altri meccanismi di immunosoppressione specifica possono essere realizzati con anticorpi monoclonali (OKT3) diretti contro la molecola CD3 dei linfociti umani.
CsA = ciclosporin
TAC = tracrolimus
SRL = sirolimus
ERL = everolimus

Cn = calcineurine (phosphatase)
mTOR = kinase (mamalian target rapamicine)
NF-AT = activator nuclear factors of T linfocits (IL2)
P70S6 = protein kinase
CyPA, Fkbp12 = immunophylline
Bioavailability increases with progression of therapy.

Children can bear proportionally higher doses than adults.

Patients with liver transplant having diarrhea have impaired absorption.

Food influences absorption: eg grapefruit increases cyclosporin and tacrolimus concentration.
| DRUGS THAT: | Decrease CsA concentration |
| DRUGS THAT: | Increase CsA concentration |
| DRUGS THAT: | Reduce renal function |

**Pharmacological interactions with Ciclosporin (CsA)**

<table>
<thead>
<tr>
<th>Decrease CsA concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenitoina o fenobarbital</td>
</tr>
<tr>
<td>Carbamazepina</td>
</tr>
<tr>
<td>Isoniazide</td>
</tr>
<tr>
<td>Rifampicina</td>
</tr>
<tr>
<td>Trimethoprim/sulfametossazolo per uso endovenoso</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Increase CsA concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazolo</td>
</tr>
<tr>
<td>Eritromicina</td>
</tr>
<tr>
<td>Steroidi</td>
</tr>
<tr>
<td>Metilprednisolone</td>
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<tr>
<td>Diltiazem</td>
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<td>Verapamil</td>
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</tbody>
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<thead>
<tr>
<th>Reduce renal function</th>
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<tr>
<td>Aminoglicosidici</td>
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<td>Melfalan</td>
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<td>Anfotericina 3</td>
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<td>Trimethoprim/sulfametossazolo</td>
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St. John's wort  
(Hypericum perforatum)

Mechanism of action
MAO inhibition, reuptake inhibition 5HT, NA, DA, GABA, Glu

Collateral mechanisms
P-glycoprotein substrate (transfer: absorption, elimination, distribution
and extrudes drugs from cells) and activity induction (intestine, kidney, liver, testicles, brain, blood tissues)
CYP3A4 and CPY1A2 induction

Interactions
- ciclosporine
- digossine
- teophilline
- indinavir
- warfarine
- amitriptiline
- contraceptives
- paroxetine
**Tocilizumab (monoclonal antibody)**

Treatment of patients with **rheumatoid arthritis** (RA). Studied as a treatment for **Crohn's disease** and **systemic lupus erythematosus**