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Manual of

Rational Skin Therapy and Dermatological Drugs

Sanjay Ghosh
Partha Mukherjee
Sanjib Chowdhuri
Subhadeep Mallick
Sujata

2nd Edition

JAYPEE

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CHAPTER

2

Systemic Drugs

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SYSTEMIC CORTICOSTEROIDS

Glucocorticoids are the cornerstone of dermatological therapy because of their anti-inflammatory and immunosuppressive properties. They have a basic four ring structure of cholesterol with one pentane and three hexane rings. Systemic steroids are synthetic derivatives of natural steroid cortisol, produced by adrenal glands. Different systemic steroids have different potencies, glucocorticoid and mineralocorticoid actions and duration of action.

Classification

	Glucocorticosteroid potency	Mineralocorticoid potency	HPA Suppression	Span of action (in hours)	Plasma half-life (in minutes)	Glucocorticoidequivalent dose (mg)
Short-acting						
Cortisone	0.8	0.8		8–12	80–118	25
Hydrocortisone	1	1	1	8–12	90	20
Intermediate-acting						
Prednisone	4	0.25	4	24–36	60	5
Prednisolone	4	0.25		24–36	115–200	5
Methylprednisolone	5	0	4	24–36	180	4
Triamcinolone	5	0	4	24–36	78–188	4
Long-acting						
Dexamethasone	25–30	0	17	36–54	100–300	0.75
Betamethasone	25–40	0		36–54	100–300	0.6

Indications

Autoimmune bullous dermatosis

- Pemphigus vulgaris
- Bullous pemphigoid
- Cicatricial pemphigoid
- Gestational pemphigoid
- Linear IgA bullous dermatosis
- Epidermolysis bullosa acquisita
- Erythema multiforme major
- Controversial use—Stevens–Johnson syndrome/toxic epidermal necrolysis

Autoimmune connective tissue disorders

- Lupus erythematosus
- Dermatomyositis
- Mixed connective tissue disorders
- Eosinophilic fasciitis
- Relapsing polychondritis
- Systemic sclerosis (selective cases)
- Morphea (generalized)

Vasculitis

- Cutaneous
- Systemic

Neutrophilic dermatosis

- Pyoderma gangrenosum
- Sweet syndrome
- Behcet's disease

Dermatitis

- Contact dermatitis
- Atopic dermatitis (flare)
- Photodermatitis
- Exfoliative erythroderma

Papulosquamous disorders

- Lichen planus

Miscellaneous

- Type 1 and type 2 reactions in leprosy
- Sarcoidosis
- Severe urticaria/angioedema
- DRESS

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- Arthropod bites
- Androgen excess (hirsuitism/recalcitrant acne vulgaris)
- Postherpetic neuralgia prevention (controversial use)

Oral mini pulse

- Vitiligo Alopecia areata (progressive with >50% scalp involvement)
- Lichen planus

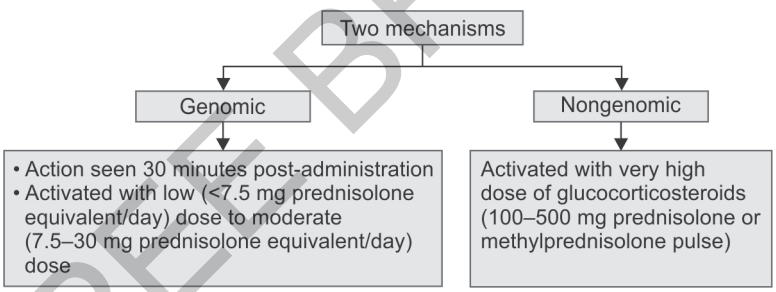
Intramuscular corticosteroid indications

- Dermatitis: contact dermatitis, nummular eczema
- Papulosquamous disorders: lichen planus
- Urticaria
- Prurigo nodularis

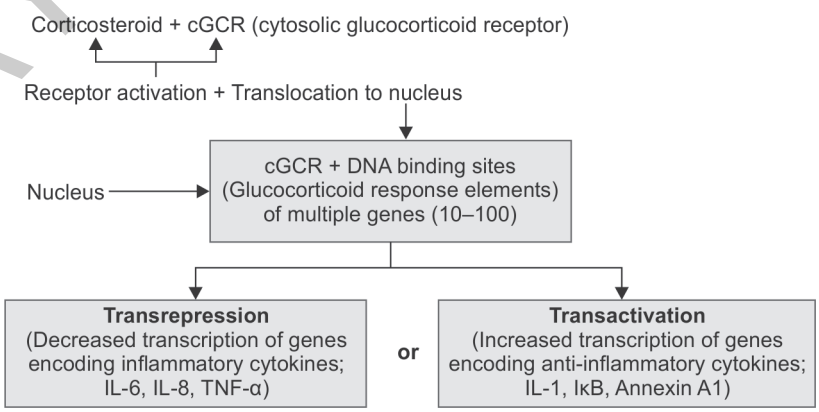
Intralesional injections indications

- Alopecia areata
- Granulomatous cheilitis
- Granuloma annulare
- Hemangiomas
- Hypertrophic lichen planus
- Keloid
- Lichen sclerosus
- Lichen simplex chronicus
- Nodular scabies
- Nodulocystic acne
- Prurigo nodularis
- Intravenous pulse therapy indications
- Autoimmune bullous disorders: Pemphigus vulgaris, bullous pemphigoid
- Neutrophilic dermatosis: Pyoderma gangrenosum, sweet syndrome
- Systemic vasculitis

Mechanism of Action



Genomic Mechanism



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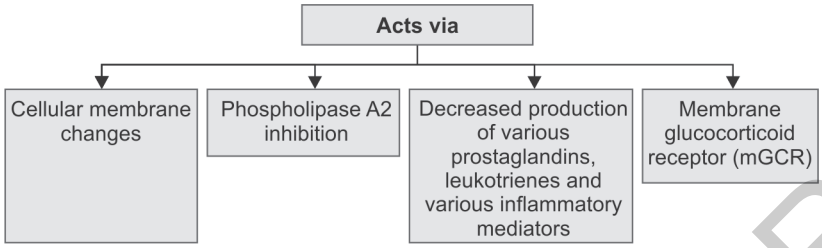
Nongenomic Mechanism



Additional Mechanism of Action

Angiogenic effects: Causes vasoconstriction, decreases angiogenesis and permeability.

Dosage

- Intralesional: 10–40 mg/mL triamcinolone once every 3–4 weekly, methyl prednisolone (depot) 10 mg every 4–8 weeks, hydrocortisone (depot) 25 mg every 4 weeks.
- Intramuscular: 10–40 mg/mL triamcinolone deep IM; longer acting agents like triamcinolone acetonide and methylprednisolone acetate (40–160 mg) to be used 4–6 times/year, chances of HPA axis suppression is high.
- Oral: 2.5 to >100 mg of prednisolone of equivalent. In majority of dermatological disorders an initial dose of 40–60 mg/day in average weight adults or 1 mg/kg/day in children is effective.
- Oral minipulse: Betamethasone or dexamethasone 5 mg as single dose on two consecutive days per week.
- Intravenous and pulse therapy: Methylprednisolone being highly potent with low sodium retaining activity is preferred as pulse therapy in a dose of 500 mg–1 g daily over 2 hours for 1–5 days. Dexamethasone 100 mg IV on 3 consecutive days is also used.

Monitoring

Baseline Checklist (planning for long-term therapy).

History

- Family history of diabetes, hypertension, dyslipidemia, heart disease
- Vaccination history (hepatitis A, B, influenza, tetanus toxoid, varicella zoster, HPV, *Streptococcus pneumoniae*)
- Examination
- BP and body weight measurement
- Eye examination for cataract
- Height and weight plotted on growth chart for children

Laboratory investigations

- Tuberculosis screening: Mantoux test, chest X-ray, interferon-γ-releasing assay
- Triple serology: Hepatitis B, C, HIV
- Fasting blood sugar, HbA1c
- Triglycerides
- Potassium levels
- Measurement of bone density

Follow-up (at 1 month and every 2–3 months)

- Body weight and BP measurements
- Height and weight on growth curve for children
- Eye check up in every 6 months

Laboratory investigations (at 1 month and every 3–4 months)

- Serum electrolytes (mainly potassium)
- Blood sugar (fasting)
- Triglycerides
  - Before stopping therapy: Cortisol levels (AM)

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Adverse Effect

Short Term

- Acneiform eruptions
- Increased risk of infections
- Impaired wound healing
- Gastrointestinal intolerance
- Increased appetite, weight gain
- Fluid/sodium retention/hypokalemia
- Hyperglycemia
- Mood fluctuations, anxiety, insomnia
- Muscle weakness
- Amenorrhea

Long Term

Cutaneous

- Atrophy, striae, telangiectasia
- Vascular fragility, purpura Infections
- Acne, acneiform eruptions
- Cutaneous infections (Staphylococcal, herpes)
- Hirsutism

Musculoskeletal

- Osteoporosis
- Osteonecrosis (most common site: proximal femur, used for at least 6–12 months may lead to development)
- Muscle atrophy
- Myopathy
- Growth retardation

Ophthalmologic

- Cataracts
- Glaucoma
- Hemorrhage
- Exophthalmos
- Infection

Gastrointestinal

- Nausea
- Vomiting
- Gastroesophageal reflux
- Peptic ulcer disease
- Intestinal perforation
- Pancreatitis
- Fatty liver changes

Metabolic

- Hyperglycemia
- Hypertension
- Hypokalemia
- Weight gain/obesity/cushingoid changes
- Hypertriglyceridemia
- Hypocalcemia

Neuropsychiatric

- Peripheral neuropathy
- Seizures
- Pseudotumor cerebri
- Epidural lipomatosis
- Mood changes (euphoria/irritability/mania/depression)
- Steroid phobia

Cardiovascular

- Hypertension
- Atherosclerosis
- Peripheral edema

Gynecological

- Amenorrhea

Hematologic

- Leukocytosis
- Eosinopenia
- Lymphopenia

Infections

- Tuberculosis reactivation
- Opportunistic—deep fungal
- Prolonged herpes virus infections

Endocrinal

- HPA axis suppression:
  - Steroid withdrawal syndrome
  - Addisonian crisis.

Pulse IV Therapy

- Cardiac arrhythmia
- Seizures
- Electrolyte abnormality

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Intramuscular Therapy

- At injection site: Pain, bleeding, subcutaneous fat atrophy, cold abscess, crystal deposition
- Others: purpura, menstrual abnormalities

Intralesional Therapy

- Immediate: Pain, bleeding, infection (rarely abscess).
- Subsequent: Atrophy, telangiectasia, hypopigmentation, hypertrichosis, stellate pseudoscars, secondary infection.

High risk patients for glucocorticoid toxicity

- Female patients, postmenopausal women and elderly.
- Children
- Patients of autoimmune connective tissue disorders like SLE, dermato/polymyositis, rheumatoid arthritis.
- Liver disorders
- Hypoalbuminemia
- Smokers and alcoholics

Drug Interactions

- Antidiabetics (insulin and oral hypoglycemics): Increase in blood sugar level.
- NSAIDs: Risk of peptic ulcer disease and GI hemorrhage is increased.
- Immunosuppressives (biologics, JAK inhibitors, conventional immunosuppressives like azathioprine, cyclosporine, mycophenolate): Chance of severe infections, myelosuppression.
- Anticoagulants: Anticoagulant effect of warfarin increased.
- Potassium losing diuretics (loop diuretics, thiazides) and inotropic agents (digoxin): Increased risk of hypokalemia.
- Macrolides and azole antifungals: Increase corticosteroid levels through CYP 3A4 inhibition.
- Hormonal contraceptives: CYP3A4 substrates and increase corticosteroid levels.

Drugs reducing corticosteroid levels:

- Rifampicin, phenytoin, carbamazepine, phenobarbital (by induction of CYP3A4)
- Isoniazid
- Cholestyramine: By decreasing absorption

Contraindications

Absolute

- Hypersensitivity
- Herpes simplex keratitis
- Systemic fungal infections

Caution

- Cardiovascular: Hypertension, congestive heart failure, fluid overload
- Psychiatric: Prior psychosis, severe depression
- Infections: Tuberculosis, viral and other active infections
- GI: Peptic ulcer disease, inflammatory bowel disease, diverticulitis
- Musculoskeletal: Osteoporosis, myopathy
- Metabolic: Diabetes mellitus
- Ocular: Cataract, glaucoma
- Vaccinations: Live vaccines to be avoided for at least 1 month in patients receiving high dose of glucocorticoids (prednisolone ≥20 mg or dose equivalent of ≥2 mg/kg body weight in children weighing <10 kg) for >2 weeks. Inactive vaccines can be given 2 weeks prior to starting steroids.

Hypothalamic-Pituitary-Adrenal Axis Suppression and Corticosteroid Tapering

- Basal daily cortisol secretion by adrenal cortex is 20–30 mg/day which is equivalent to about 5–7.5 mg prednisolone daily.
- Dose and duration of glucocorticoid therapy determines the susceptibility to HPA-axis suppression. Doses substantially exceeding the physiological levels for more than 3 weeks can cause mild HPA-axis suppression.
- Chances of HPA-axis suppression is more with long-acting preparations than with short or intermediate acting ones.

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- Systemic corticosteroid therapy should continue during periods of stress like trauma, surgery or infection with higher doses needed for up to 3 days during acute stress to avoid acute adrenal crisis.
- Morning cortisol levels may need 6–9 months to return to normal following stoppage of long-term high dose corticosteroid therapy, however, the hypothalamus recovers within 14–30 days.
- Tapering of corticosteroids is essential to help the HPA-axis to recover promptly.
- Tapering schedule for GC when used for > 3–4 weeks

Prednisolone (or equivalent)

- >40 mg/d: reduce 5–10 mg weekly
- 20–40 mg/d: reduce 5 mg weekly
- 10–20 mg/d: reduce by 2.5 mg weekly
- 5–10 mg/d: reduce by 1 mg every 2–3 weeks
- Monitoring of disease activity is essential along with attempts at steroid tapering.

Pregnancy: Category C.

Lactation

- Safe, though small amounts excreted in breast milk doses up to 40 mg/day rarely cause systemic effects in infants.

Children

- Long-term steroid use can lead to growth suppression in children.
- Normal growth in children with 1m2 surface area can be attained with 5 mg of prednisolone per day.

SYSTEMIC IMMUNOSUPPRESSIVE AND IMMUNOMODULATORY AGENTS

Methotrexate

Methotrexate, remains one of the most common anti-metabolite, cytotoxic agents used in dermatology. It has both immunosuppressive and anti-proliferative properties. Structurally it is 4–amino-N^{10}–methylpteroylglutamic acid.

Indications

Approved Indication (FDA)

- Severe psoriasis with or without psoriatic arthritis.
- Sezary syndrome

Unlicensed Indications

Papulosquamous disorders

- Pityriasis rubra pilaris
- Pityriasis lichenoides et varioliformis acuta
- Lichen planus

Immunobullous disorders

- Pemphigus vulgaris
- Bullous pemphigoid
- Mucous membrane pemphigoid
- Epidermolysis bullosa acquisita

Autoimmune connective tissue disorders

- Systemic lupus erythematosus
- Subcutaneous lupus erythematosus
- Dermatomyositis
- Systemic sclerosis
- Morphea

Vasculitis

- Cutaneous small vessel vasculitis
- Cutaneous polyarteritis nodosa
- Kawasaki disease
- Behcet disease

Neutrophilic dermatoses

- Pyoderma gangrenosum

Lymphoproliferative disorders

- Cutaneous T cell lymphoma
- Mycoses fungoides
- Lymphomatoid papulosis

Dermatitis

- Atopic dermatitis

Miscellaneous

- Alopecia areata
- Chronic idiopathic urticaria

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- Cutaneous Crohn disease
- Generalized granuloma annulare
- Hailey-Hailey disease
- Keratoacanthoma
- Langerhans cell histiocytosis
- Necrobiosis lipoidica
- Prurigo nodularis
- Reiter disease
- Sarcoidosis
- Scleredema diabeticorum

Pharmacology

Methotrexate is a weak organic acid and can be administered orally, intramuscularly, intravenously and subcutaneously. Mean oral bioavailability is 33% with intramuscular bioavailability around 76%. Milk based food intake can reduce bioavailability in children, though not in adults. It is excreted mainly through kidneys with a terminal half-life of 3–10 hours. Methotrexate is a slow acting drug with full clinical benefit seen in 2–3 months.

Mechanism of Action

- Cytotoxic effects: It competitively inhibits the enzyme dihydrofolate reductase hampering the formation of cofactor tetrahydrofolate. This prevents the synthesis of thymidylate and purine nucleotides need for both DNA and RNA synthesis. A delayed effect occurring 24 hours after methotrexate administration is the partially reversible, competitive inhibition of thymidylate synthetase. The net result is inhibition of the S phase of cell division.
- Immunosuppressive effects: Mediated through DNA synthesis inhibition in immunologically competent cells.
- Anti-inflammatory effects: Inhibition of conversion of AICAR (5–aminoimidazole 4–carboxamide ribonucleotide) to formyl-AICAR by methotrexate results in its intracellular accumulation. This increases local tissue concentration of anti-inflammatory adenosine, which reduces pro-inflammatory cytokines like TNF-α,IL-6,8 and decreases reactive oxygen species. Methotrexate also inhibits methionine synthase, thus decreasing pro inflammatory S-adenyl methionine.

Dosage

- Oral: 7.5–25 mg PO weekly as single dose
- Weinstein Frost regimen: 2.5–7.5 mg every 12 hourly for three doses weekly (8 AM and 8 PM on 1st day and 8 AM on 2nd day).
- Both dosing regimens are equally effective, however split dosing may lessen GI side effects.
- Parenteral: 10–25 mg IM or IV once weekly. 7.5–30 mg in pre pen filled devices are used for subcutaneous injections.

The initial starting dose depends on the patients age, renal function and associated comorbidities. An initial test dose of 2.5–5 mg is given in elderly and patients with renal impairment with a complete blood count and liver function test done after 1 week for early detection of myelosuppression and hepatic injury. In low-risk patients an initial starting dose of 10–15 mg weekly with gradual increments of 2.5 to 5 mg every 2–4 weeks until 25 mg weekly dose is reached with minimal toxicity.

Switching from oral to parenteral route can result in increased bioavailability of the drug, so adequate dose reduction with monitoring of blood parameters for 2 weeks after switching is preferable.

Monitoring

Baseline laboratory monitoring

- CBC with platelet count
- LFT
- Serology for Hep B, C and HIV

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- BUN and creatinine
- TB quantiferon gold
- Pregnancy test for women of child bearing potential
- Chest X-ray.

During Therapy

- CBC, platelet count and LFT-1–3 weeks after initiation and after each dose escalation, then monthly for 2–4 months, and then every 3–4 months, if stable.
- Renal function tests: Once or twice yearly
- Fibroscan along with LFT are the primary screening test to assess Methotrexate induced liver injury in patients on long term therapy. Fibroscan is done 1 year after start of therapy and then repeated yearly.
- Other noninvasive test to detect liver fibrosis include NASH Fibrosure,pro-collagen III, fibrosis 4 (FIB-4), fibrospect II, fibrometer, hepatic USG and Magnetic resonance elastography.
- Liver biopsy, though considered gold standard is rarely needed after 3.5–4 g of cumulative dosage.
- In male patients serum ferritin to exclude hemochromatosis and antimitochondrial antibodies in females to rule out primary biliary cirrhosis.

Risk Factors for Patients Developing Hepatotoxicity on Methotrexate

- Persistent deranged LFT
- History of chronic hepatitis B or C or other liver disease
- Past or present history of excessive alcohol intake
- Family history of inheritable liver disease
- Obesity
- Diabetes mellitus
- Hyperlipidemia
- History of intake of hepatotoxic drugs and chemicals
- No folate supplementation

Adverse Effect

- Hematologic: Bone marrow suppression is the most important acute adverse effect. Leucocyte and platelet counts are reduced maximally within 7–10 days after starting treatment. The main risk factors for pancytopenia are old age, patients with renal disorders, hypoalbuminemia(<3 g/dL),lack of folate supplementation and simultaneous administration of drugs like NSAIDs and trimethoprim-sulfamethoxazole. Folic acid supplementation (1–5 mg/d) helps in preventing myelosuppression. If WBC count is <3,500/mm^3 and platelet count is <1 lakh/mm^3 dose reduction or discontinuation of methotrexate is advised with restart of treatment at lower dose after 2–3 weeks gap following correction of laboratory abnormalities.
- Hepatic effects: Hepatotoxicity with chances of liver fibrosis are significantly more with long term methotrexate therapy. Risk of liver injury is low with cumulative dose <1.5 g. Methotrexate induced liver cirrhosis risk varies between 0–25%. Dose of the drug needs to be reduced if transaminases exceed 2–3 fold the normal values and the drug has to be discontinued if the values are >5 times normal.
- Pulmonary effects: Acute pneumonitis and pulmonary fibrosis, pulmonary toxicity is idiosyncratic.
- GIT effects: Anorexia, nausea, vomiting, diarrhea and ulcerative stomatitis. Ulcerative stomatitis and severe diarrhea need stoppage of treatment. Folate supplementation reduces GI side effects without compromising the efficacy.
- Mucocutaneous effects: Oral ulceration, stomatitis, cutaneous ulceration over lower legs may indicate myelosuppression. Rapid ulceration of methotrexate treated psoriatic plaques also suggest toxicity.

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Methotrexate 'recall reaction' may occur at sites of prior irradiation or recent sunburn. Mild alopecia, acral erythema, epidermal necrosis and vasculitis are other cutaneous side effects.

- Carcinogenic effects: Lymphoma and lymphoproliferative disorders rarely reported, though no statistical evidence of increased risk of malignancy seen with methotrexate use in dermatological disorders.
- Reproductive effects: Category X drug and is to be strictly avoided in pregnancy. Women of reproductive age group should use the drug with proper birth control measures. Men can show reversible oligospermia and should avoid impregnating a woman while on methotrexate. Men are to wait 3 months after stopping the drug and women 1 complete menstrual cycle before attempting conception.
- Opportunistic infections: Pneumocystis pneumonia, histoplasmosis and cryptococcosis have been reported.
- Antidote for Methotrexate toxicity: Leucovorin is the reduced active form of folic acid. Leucovorin is particularly effective in preventing myelosuppression, gastrointestinal toxicity, and neurotoxicity during methotrexate treatment. Leucovorin dose for methotrexate overdose is 10 mg/m^2 orally, IM, or IV every 6 hours, starting immediately after overdose or within 24 hours if delayed methotrexate elimination.

Drug Interactions

- Drugs increasing methotrexate levels and toxicity: Aromatic anticonvulsants (phenytoin), tetracyclines, antipsychotics (phenothiazines), anti-inflammatory drugs (aspirin, NSAIDs), loop diuretics (furosemide), and antiplatelet drugs (dipyridamole).
- Drugs decreasing methotrexate absorption and thus efficacy: Cholestyramine.
- Drugs increasing risk of hepatotoxicity: Retinoids, alcohol.
- Drugs increasing hematologic toxicity: Dapsone, sulfonamides, trimethoprim, cidofovir, zidovudine, azathioprine.
- Immunosuppressives (biologics, JAK inhibitors, conventional immunosuppressants): Increase risk of infections and/or myelosuppression.

Contraindications

Absolute

- Hypersensitivity to methotrexate or components of formulation
- Pregnancy (category X)
- Lactation
- Myelosuppression

Relative

- Renal/hepatic dysfunction
- H/O alcoholism
- Hematological disorders
- Active infection and/or reactivation of infection(tuberculosis)
- Diabetes mellitus
- Obesity
- Recent vaccination with a live vaccine
- HIV infection
- Men and women wanting to conceive.

Pregnancy Category

- Category X

Lactation Category

- Absolutely contraindicated as excreted in breast milk.

Children

Children: Used off label in children with initial dose of 0.2 mg/kg once weekly which can be increased to 0.5 mg/kg (max 25 mg) according to clinical response.

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CYCLOSPORINE

Cyclosporine or cyclosporine A (CsA) is a lipophilic and highly hydrophilic cyclic undecapeptide of 11 amino acids, isolated from the soil fungus *Tolypocladium inflatum gams*. Its immunosuppressive properties had been first used in organ transplant recipients to prevent rejection. Subsequently it has been used as an immunomodulator in a number of dermatological disorders.

Indications

Approved indications

- Psoriasis (as intermittent short-term therapy, or rescue therapy for severe flare ups and long term maintenance therapy).
- Severe Atopic dermatitis (adults and children >2 years of age).

Unlicensed indications

- Neutrophilic dermatoses: Pyoderma gangrenosum, Behcet disease
- Chronic idiopathic urticaria (especially auto-immune urticaria)
- Severe adverse cutaneous drug reactions – Stevens-Johnson Syndrome (SJS)/Toxic epidermal necrolysis (TEN)
- Bullous disorders – Pemphigus and its variants, bullous pemphigoid, linear IgA bullous dermatosis, epidermolysis bullosa acquisita.
- Autoimmune connective tissue disorders – Dermatomyositis, SLE, scleroderma
- Papulosquamous disorders – Lichen planus, lichen planopilaris, pityriasis rubra pilaris.
- Granulomatous dermatoses – Granuloma annulare, sarcoidosis
- Alopecia areata
- Photosensitivity dermatoses – Chronic actinic dermatitis
- Prurigo nodularis
- Chronic graft versus host disease.

Mechanism of Action

Cyclosporine + cyclophilin (intracytoplasmic immunophilin) = Cyclosporine-cyclophilin complex

Cyclosporine-cyclophilin complex + calcineurin (calcium dependent serine/threonine phosphatase) inhibits

↓

Dephosphorylation of nuclear factor of activated T cells (NFAT-1).

Calcineurin inhibition by cyclosporin thus leads to reduced action of transcription factor NFAT-1, blocking the production of pro-inflammatory cytokines, and chemokines like interleukin2(IL 2),IL4, interferon γ (IFN-γ), tumour necrosis factor α (TNF-α).

Pharmacology

Absorption of cyclosporine following oral administration depends on the formulation used and patient specific characteristics. The bioavailability of the microemulsion form is 10–54% more than the original non-emulsified form.

The microemulsion form has shown a more rapid response, higher remission rates in the first 8 weeks, and a 10% lower dose to maintain efficacy compared to the nonemulsified formulation.

Peak plasma concentrations occur 2–4 hours after administration and higher serum concentration of cyclosporine is produced when the drug is administered before meals.

Cyclosporine is metabolized by hepatic cytochrome P450 3A4 enzyme (CYP3A4). The elimination half-life is 6–18 hours with more than 90% of the drug undergoing biliary excretion with only 6% being eliminated through urine.

Monitoring

Baseline monitoring

Complete history and physical examination to rule out active infections, hypertension,

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kidney disease, and malignancy are needed before initiating therapy. Two baseline blood pressure measurements at least a day apart should also be done

Baseline screening	Follow up monitoring
• Two serum creatinine levels at least 1 day apart • CBC with platelet count • Blood urea nitrogen • Electrolytes – potassium, magnesium • Uric acid • Urinalysis with microscopy • Liver function test • Fasting lipid profile	• Blood pressure must be monitored every 2 weeks for first 3 months and if stable then monthly. • CBC with platelet counts at 1 month, then every 2–4 months • Blood urea nitrogen, creatinine, magnesium, potassium-every 2 weeks for 1–2 months, then monthly or every 3 months if stable • LFT – monthly • Urinalysis with microscopy-every monthly if abnormal, otherwise yearly • Fasting lipid profile every 2–4 weeks for 1–2 months, then every 3 months if stable

Dosage

In adults for dermatological indications cyclosporine is used in doses between 2.5–5 mg/kg/day and the pediatric dose is 5–7 mg/kg/d.

Continuous use for up to 1 year is recommended by FDA while worldwide consensus guidelines recommend continuous use for up to 2 years.

Ideal body weight should be used to calculate dosage in obese patients as dose calculations based on actual body weight can lead to excessive dosage.

If serum creatinine remains raised by >30% of baseline over 2 weeks then dose of cyclosporine is to be lowered by 1 mg/kg/d for at least 1 month. If creatinine decreases to <30% above baseline then continue cyclosporine at new dosage. Creatinine persisting above 30% of baseline still, then cyclosporine needs to be stopped. Cyclosporine can be restarted at lower dosage if creatinine returns to within 10% of baseline.

Adverse Effect

Renal

- Nephrotoxicity is one of the most important adverse effects of cyclosporine and renal dysfunction occurs in 25% of patients
- 2 types: 1st type-within 2–3 weeks of starting the drug and is associated with reduced glomerular filtration rate along with hypertension and tubular dysfunction, reversible.
- 2nd type-subclinical chronic nephrotoxicity, irreversible, seen with long term use >6 months.
- Cardiovascular
- Hypertension is usually mild and reversible after dose reduction or discontinuation of cyclosporine.
- Neurologic – most common adverse effects in patients using cyclosporine for less than 2 months.
- Headache, tremor, confusion, paresthesia, hyperesthesia, seizures, psychosis, Pseudotumour cerebri.[12]
- Gastrointestinal: nausea, vomiting, diarrhea, anorexia.
- Mucocutaneous: hypertrichosis (seen in all patients on long term use), gum hypertrophy (>70% patients, more in children), acneiform eruptions, Keratosis pilaris, sebaceous hyperplasia, warts and epidermal inclusion cysts.
- Musculoskeletal: myalgia, lethargy, arthralgia, myopathy in transplant patients on higher doses, osteoporosis.
- Abnormalities in laboratory parameters: hyperkalemia, hypomagnesemia, hyperuricemia, hyperlipidemia, hyperbilirubinemia (rare).

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Sanjay Ghosh MD(Dermatology and Venerology) (California) is Professor, Department of Dermatology, Santiniketan Medical College, West Bengal. He is Former Professor and Head, Department of Dermatology and Venereology at MGM Medical College and LSK Hospital, Kishanganj, Bihar, India, and Former Medical Director (Honorary), Institute of Allergic and Immunologic Skin Diseases (IAISD), Kolkata, West Bengal. He was Former Vice-President of Contact and Occupational Dermatoses Forum of India (CODFI); Ex-Coordinator, Psoriasis SIG Group, IADVL; and Ex-Member, IADVL SIG Urticaria Group. He was the former editor of Indian Journal of Dermatology. He has been a past reviewer of British Journal of Dermatology, Clinical and Experimental Dermatology, Indian Journal of Dermatol, and Indian Journal of Dermatology, Venereology, and Leprology. He is the author of Atlas and Synopsis of Contact and Occupational Dermatology, Manual of Rational Skin Therapy and Dermatological Drugs, 201 Skin Diseases, and Urticaria and Angioedema Management. He has also contributed to all the past editions of IADVL Textbook of Dermatology. He is the editor of Recent Advances in Dermatology I, II and III, and CODFI Newsletter. He was awarded with Ambady Oration 2014 DERMACON ICD, Delhi; RK Panja Memorial Oration CUTICON 2013; AK Jha Oration CUTICON Bihar 2018; NRS 150 Foundation Day Oration 2022; Life Time Achievement Award: AAD India Conclave 2024; and IADVL Best Teacher Award 2025. He has been practicing in his field for over 36 years.

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