

Calcineurin inhibitors

Cyclosporine and tacrolimus, the backbone of solid-organ transplant immunosuppression and, at lower exposure, of severe autoimmune disease - two structurally unrelated molecules that converge on the same intracellular enzyme, calcineurin, and share nephrotoxicity as the property that defines their dosing far more than their indication does.

Online guide: <https://www.medguideglobal.com/pharmacology/immunomodulators/calcineurin-inhibitors>

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Quick revision

One Liner: Cyclosporine and tacrolimus bind different immunophilins but shut down the same enzyme, calcineurin, and stop T-cell activation the same way - the practical consequence is that both are dosed by measured blood level, not by weight alone, because the gap between an effective and a toxic level is narrow for both.

1. Cyclosporine binds cyclophilin and tacrolimus binds FKBP-12, but both immunophilin-drug complexes then inhibit calcineurin, blocking the dephosphorylation step needed to activate the transcription factor NFAT and, downstream, interleukin-2 gene transcription in T cells. [1][2][3]
2. Nephrotoxicity is the property that most defines both drugs' dosing: cyclosporine's historic oral-solution data recorded it in roughly a quarter to nearly two-fifths of transplant recipients depending on organ, and tacrolimus causes it through the same vasoconstrictive and tubular mechanism. [1][2]
3. Cyclosporine's two branded formulations, Sandimmune and Neoral, are explicitly not bioequivalent and cannot be substituted for each other on a milligram-to-milligram basis. [1]
4. Grapefruit and grapefruit juice raise cyclosporine blood concentrations by inhibiting its metabolism and should be avoided. [1]
5. Hirsutism and gingival hyperplasia are recognised, specifically cyclosporine-associated cosmetic adverse effects; tacrolimus does not carry the same labelled prominence for either. [1]
6. Both drugs carry posterior reversible encephalopathy syndrome (PRES) as a labelled neurotoxicity, presenting with impaired consciousness, seizures or visual disturbance. [1][2]
7. New-onset diabetes after transplant is a labelled tacrolimus risk, with African-American and Hispanic transplant recipients specifically identified as higher-risk groups. [2]
8. Both drugs increase susceptibility to infection and to lymphoma and other malignancy - a direct consequence of the immunosuppression itself, not a separate off-target toxicity. [1][2]

Overview

1. Cyclosporine and tacrolimus look nothing alike chemically - cyclosporine is a cyclic polypeptide, tacrolimus a macrolide - and each binds its own immunophilin: cyclophilin for cyclosporine, FK-binding protein 12 (FKBP-12) for tacrolimus. What makes them one pharmacological class is what happens next: both immunophilin-drug complexes inhibit the same intracellular enzyme, calcineurin, blocking the dephosphorylation of the transcription factor NFAT that T cells need to switch on interleukin-2 and other cytokine genes. Block that one step and T-cell activation and proliferation stall, regardless of which immunophilin the drug engaged to get there. [3][1][2]
2. This class carries the transplant-immunosuppression backbone role that no other drug family in the immunomodulator section shares: cyclosporine and tacrolimus prevent rejection of kidney, liver and heart allografts (and, for tacrolimus, lung), typically as part of a multi-drug regimen alongside a corticosteroid and often an antimetabolite. At much lower relative exposure, cyclosporine also has an FDA rheumatoid arthritis indication for severe disease inadequately responsive to methotrexate, and a psoriasis indication for severe, recalcitrant plaque disease that has failed other systemic therapy. [1][2]

3. Nephrotoxicity is what actually governs how both drugs are used day to day, more than the underlying indication does. Structural kidney damage is a recognised consequence of both, tracking with dose and duration, and both require the specific practice - therapeutic drug monitoring of whole-blood trough concentrations - that most other DMARDs and immunosuppressants in this section do not need. A calcineurin inhibitor is, in a very literal sense, dosed against a laboratory number rather than against a fixed regimen. [1][2]

4. The two drugs are not simply interchangeable at an equivalent dose. Cyclosporine's own two formulations, Sandimmune and the more bioavailable Neoral, are explicitly labelled as not bioequivalent and not mg-for-mg substitutable, and the cosmetic adverse effects that patients notice first - hirsutism and gingival hyperplasia - are far more a cyclosporine story than a tacrolimus one in the material reviewed here, while new-onset diabetes after transplant is a more prominently labelled tacrolimus finding. [1][2]

Classification and drug examples

Intro: Grouped by immunophilin binding partner, since that is the one mechanistic step that genuinely separates the two drugs before they converge on the same calcineurin target.

1. Name: Cyclophilin-binding calcineurin inhibitor

1. Note: A cyclic polypeptide that binds cyclophilin; the older of the two drugs, with a long transplant and rheumatologic track record.

Name: Cyclosporine (ciclosporin)

1. Neoral

2. Sandimmune

Route: Oral or intravenous

Note: Neoral and Sandimmune are not bioequivalent and cannot be substituted for each other on a milligram-to-milligram basis; also indicated for severe rheumatoid arthritis and severe plaque psoriasis, not only transplantation. [1] [1]

2. Name: FKBP-12-binding calcineurin inhibitor

2. Note: A macrolide that binds FK-binding protein 12; generally used at higher relative potency per milligram than cyclosporine and is now the more commonly used calcineurin inhibitor in solid-organ transplantation.

Name: Tacrolimus

Prograf

Route: Oral, intravenous or oral suspension

Note: Indicated for kidney, liver, heart and lung transplant prophylaxis of rejection, always in combination with other immunosuppressants. [2] [2]

Mechanism of action

Summary: Both drugs are converging-pathway immunosuppressants: they bind different intracellular immunophilins but both resulting complexes inhibit calcineurin, the phosphatase that normally activates the transcription factor NFAT. Blocking that one step prevents T cells switching on interleukin-2 and other cytokine genes, so T-cell activation, proliferation and differentiation are all suppressed together.

Target: Calcineurin (a calcium/calmodulin-dependent serine/threonine phosphatase) via cyclophilin (cyclosporine) or FKBP-12 (tacrolimus)

Cidal Static: Immunosuppressive rather than cytotoxic - the effect is reversible suppression of T-cell activation, not cell killing

Kill Kinetics: Effect tracks blood concentration closely; onset and offset are faster than the conventional or biologic DMARDs, which is part of why trough-level monitoring is central to using this class safely

1. Step: 1

1. Title: The drug enters the T cell and binds its immunophilin

1. Detail: Cyclosporine binds cyclophilin; tacrolimus binds FK-binding protein 12 (FKBP-12). These are different

proteins, so the two drugs are not simply the same molecule with a different name. [3]

2. Step: 2

2. Title: The immunophilin-drug complex inhibits calcineurin

2. Detail: Both complexes bind calcineurin and block its phosphatase activity, which is the convergence point of the whole mechanism. [3]

3. Step: 3

3. Title: NFAT stays phosphorylated and cannot enter the nucleus

3. Detail: Calcineurin normally dephosphorylates the transcription factor NFAT, allowing it to translocate to the nucleus. With calcineurin blocked, NFAT stays in the cytoplasm. [3]

4. Step: 4

4. Title: Interleukin-2 gene transcription fails to switch on

4. Detail: Cyclosporine's label states this directly: it provides specific and reversible inhibition of immunocompetent lymphocytes in the G0 and G1 phase of the cell cycle and inhibits lymphokine production and release, including interleukin-2, with T-helper cells as the primary target. [1]

5. Step: 5

5. Title: T-cell activation, proliferation and differentiation are suppressed

5. Detail: Without IL-2 and related cytokine signalling, the T-cell response that would otherwise drive allograft rejection or autoimmune inflammation is blunted - the shared endpoint both drugs reach by different immunophilin routes. [3][2]

Major clinical uses

1. Drug: Cyclosporine

1. Organism: Not applicable

1. Indication: Prophylaxis of organ rejection in kidney, liver and heart allograft transplantation

1. Line: backbone immunosuppressant

1. Note: Typically combined with a corticosteroid and often an antimetabolite as part of a multi-drug regimen. [1]

2. Drug: Cyclosporine

2. Organism: Not applicable

2. Indication: Severe active rheumatoid arthritis inadequately responsive to methotrexate

2. Line: second-line, may be combined with methotrexate

2. Note: Contraindicated in this indication where renal function is abnormal, hypertension is uncontrolled, or malignancy is present. [1]

3. Drug: Cyclosporine

3. Organism: Not applicable

3. Indication: Severe, recalcitrant plaque psoriasis in non-immunocompromised adults who failed systemic therapy or cannot tolerate alternatives

3. Line: reserve option

3. Note: Cannot be combined with PUVA, UVB, methotrexate, other immunosuppressives, coal tar or radiation therapy in this indication. [1]

4. Drug: Tacrolimus

4. Organism: Not applicable

4. Indication: Prophylaxis of organ rejection in adult and paediatric kidney, liver, heart and lung transplantation

4. Line: backbone immunosuppressant, now more widely used than cyclosporine in many transplant programmes

4. Note: Always used in combination with other immunosuppressants rather than alone. [2]

5. Drug: Calcineurin inhibitor plus mycophenolic acid analogue

5. Organism: Not applicable

5. Indication: Lupus nephritis, as part of combination immunosuppressive regimens described in rheumatology classification sources

5. Line: specialist-directed combination therapy

5. Note: Illustrates that this class extends into severe autoimmune disease beyond transplantation and classic rheumatoid arthritis. [3]

Pharmacokinetics

1. Drug: Cyclosporine (Neoral)

1. Route: Oral or intravenous

1. Absorption: Improved and more consistent bioavailability with the Neoral microemulsion formulation versus the older Sandimmune formulation

1. Csf Penetration: See prescribing reference

1. Metabolism: Hepatic, via CYP3A4

1. Elimination: Predominantly biliary/faecal

1. Dose Adjust: Renal and hepatic impairment; whole-blood trough monitoring is required for all patients; avoid grapefruit juice [1]

2. Drug: Tacrolimus

2. Route: Oral, intravenous or oral suspension

2. Absorption: Variable oral bioavailability

2. Csf Penetration: See prescribing reference

2. Metabolism: Hepatic, via CYP3A4

2. Elimination: Predominantly biliary/faecal

2. Dose Adjust: Lower end of the dosing range considered for patients with pre-existing renal impairment receiving a liver, heart or lung transplant; whole-blood trough monitoring required; concomitant CYP3A inhibitors (e.g. azole antifungals, macrolides) raise levels, and other nephrotoxic drugs compound renal risk [2]

1. This page gives no dose regimens by design. Dosing is individualised to indication, organ transplanted, concomitant immunosuppressants and measured blood levels, and belongs in a current prescribing reference used by the treating clinician.

2. Both drugs are metabolised substantially by CYP3A4, which is why azole antifungals, macrolide antibiotics, calcium channel blockers and many other CYP3A4-active drugs are significant interaction partners for this class, and why grapefruit juice specifically is called out as something to avoid with cyclosporine. [1][2]

3. Therapeutic drug monitoring of whole-blood trough concentrations is not an optional refinement for either drug - it is how the gap between under-immunosuppression (rejection or disease flare) and toxicity (nephrotoxicity, neurotoxicity) is actually managed in practice. [2]

Adverse effects

1. Effect: Hypertension

1. Detail: A common cyclosporine side effect which may persist during treatment. [1]

2. Effect: Hirsutism

2. Detail: Reported in roughly a fifth to a quarter of cyclosporine-treated transplant recipients. [1]

3. Effect: Gingival hyperplasia

3. Detail: Reported in about 4 to 9% of kidney and liver transplant patients on cyclosporine, and made worse by concurrent nifedipine. [1]

4. Effect: Hyperkalaemia

4. Detail: Reported occasionally with cyclosporine, sometimes with hyperchloraemic metabolic acidosis, and monitored for with tacrolimus as well. [1][2]

1. Effect: Nephrotoxicity

1. Detail: A defining risk for both drugs. Historic Sandimmune oral-solution data recorded nephrotoxicity in about 25% of renal transplant recipients, 38% of cardiac transplant recipients and 37% of liver transplant recipients; tacrolimus

causes acute or chronic kidney injury through renal vasoconstriction and direct tubular toxicity.

1. Action: Renal function is monitored throughout treatment with either drug, and dose is adjusted against measured trough levels and creatinine rather than left fixed. [1][2]
2. Effect: Hepatotoxicity
2. Detail: Cyclosporine has caused cholestasis, jaundice, hepatitis and liver failure, with fatal outcomes reported in some transplant patients.
2. Action: Liver function is monitored on a scheduled basis; new jaundice or abdominal pain is reported to the treating clinician promptly. [1]
3. Effect: Neurotoxicity, including posterior reversible encephalopathy syndrome
3. Detail: Encephalopathy including PRES has been described with both drugs, with impaired consciousness, convulsions and visual disturbance among the manifestations.
3. Action: New neurological symptoms during treatment are an urgent reason to seek medical attention; discontinuation may be necessary. [1][2]
4. Effect: Infection and malignancy from immunosuppression
4. Detail: Both drugs increase susceptibility to bacterial, viral, fungal and protozoal infection, including opportunistic infection that may be fatal, and both increase the risk of lymphoma and other malignancy, particularly of the skin - cyclosporine's psoriasis-trial data recorded skin tumours in 2.2% of 1,439 patients.
4. Action: This risk is why regular skin examination and infection vigilance are part of routine follow-up for anyone on this class, coordinated by the treating clinician rather than self-managed. [1]
5. Effect: New-onset diabetes after transplant
5. Detail: A labelled tacrolimus risk, with African-American and Hispanic transplant recipients specifically identified as facing elevated risk.
5. Action: Blood glucose monitoring is part of routine tacrolimus follow-up. [2]
6. Effect: QT prolongation
6. Detail: Tacrolimus may cause cardiac arrhythmia through QT prolongation and is avoided in patients with congenital long QT syndrome.
6. Action: Cardiac risk is assessed before starting, and the drug is avoided in this specific congenital condition. [2]
1. Drug: Cyclosporine
1. Effect: Hirsutism and gingival hyperplasia are prominent, specifically labelled cosmetic adverse effects not carrying the same labelled emphasis for tacrolimus in the material reviewed here. [1]
2. Drug: Tacrolimus
2. Effect: New-onset diabetes after transplant and QT prolongation are more prominently labelled for tacrolimus than for cyclosporine in the material reviewed here. [2]

Contraindications, precautions and interactions

1. Cyclosporine: known hypersensitivity to cyclosporine or its formulation ingredients. [1]
2. Cyclosporine in rheumatoid arthritis or psoriasis specifically: abnormal renal function, uncontrolled hypertension, or malignancy. [1]
3. Cyclosporine in psoriasis specifically: concurrent PUVA, UVB, methotrexate, other immunosuppressives, coal tar or radiation therapy. [1]
4. Tacrolimus: known hypersensitivity to tacrolimus, and the injectable formulation specifically in patients hypersensitive to HCO-60 (polyoxyl 60 hydrogenated castor oil). [2]
1. Grapefruit and grapefruit juice raise cyclosporine blood concentrations by affecting its metabolism and should be avoided. [1]
2. Sandimmune and Neoral are not bioequivalent and cannot be used interchangeably without clinical supervision and re-monitoring. [1]
3. Congenital long QT syndrome is a reason for caution with tacrolimus specifically. [2]

4. Pre-existing renal impairment in a liver, heart or lung transplant recipient is a reason to consider the lower end of the tacrolimus dosing range. [2]

1. With: Strong CYP3A4 inhibitors (azole antifungals, macrolide antibiotics, some calcium channel blockers)

1. Effect: Raise blood concentrations of both cyclosporine and tacrolimus, increasing toxicity risk. [1][2]

2. With: Other nephrotoxic drugs (aminoglycosides, amphotericin B, NSAIDs)

2. Effect: Compound the nephrotoxicity risk of either calcineurin inhibitor. [2]

3. With: Grapefruit juice

3. Effect: Specifically raises cyclosporine concentrations and is avoided. [1]

Comparison tables

Title: Same enzyme, different immunophilin, different signature toxicity

Caption: Both drugs converge on calcineurin, but the labelled adverse-effect emphasis differs. Choice of agent and dosing belong to the treating clinician.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: immunophilin

2. Label: Immunophilin bound

3. Key: signature

3. Label: Signature labelled toxicity

4. Key: extra

4. Label: Beyond transplantation

1. Drug: Cyclosporine

1. Immunophilin: Cyclophilin

1. Signature: Hirsutism, gingival hyperplasia, hypertension

1. Extra: Severe rheumatoid arthritis and severe plaque psoriasis indications [1]

2. Drug: Tacrolimus

2. Immunophilin: FKBP-12

2. Signature: New-onset diabetes after transplant, QT prolongation

2. Extra: Transplant immunosuppression only among the indications reviewed here [2]

High-yield exam pearls

1. Pearl: Different immunophilin, same downstream target - calcineurin is the convergence point.

1. Why: Cyclosporine binds cyclophilin and tacrolimus binds FKBP-12, but both complexes inhibit calcineurin and block NFAT-driven interleukin-2 transcription, which is the single fact that actually makes them one drug class. [3]

2. Pearl: Nephrotoxicity, not the indication, is what drives calcineurin-inhibitor dosing.

2. Why: Both drugs require whole-blood trough monitoring specifically because the effective and toxic ranges sit close together, unlike most of the other DMARD classes in this section. [1][2]

3. Pearl: Sandimmune and Neoral are not the same drug at the same dose.

3. Why: The label states plainly that the two cyclosporine formulations are not bioequivalent and cannot be substituted milligram-for-milligram. [1]

4. Pearl: Grapefruit juice is a cyclosporine-specific interaction worth remembering by name.

4. Why: It raises cyclosporine blood concentrations by affecting its metabolism and is explicitly flagged for avoidance in the label. [1]

5. Pearl: Hirsutism and gum overgrowth point toward cyclosporine; new-onset diabetes and QT prolongation point toward tacrolimus.

5. Why: These are the drug-specific adverse-effect signatures within a class whose core mechanism is otherwise

identical. [1][2]

Common exam traps

1. Trap: Assuming cyclosporine and tacrolimus are chemically related because they act the same way.
1. Correction: Cyclosporine is a cyclic polypeptide and tacrolimus a macrolide - structurally unrelated molecules that happen to converge on the same calcineurin target through different immunophilins. [3]
2. Trap: Treating any dose of cyclosporine or tacrolimus as interchangeable across formulations or between the two drugs.
2. Correction: Sandimmune and Neoral cyclosporine are explicitly not bioequivalent, and cyclosporine and tacrolimus are not interchangeable at an equivalent milligram dose; both require their own trough-level target. [1]
3. Trap: Believing calcineurin inhibitors are used only in transplantation.
3. Correction: Cyclosporine carries its own FDA indications in severe rheumatoid arthritis and severe plaque psoriasis, and this class also appears in specialist regimens for lupus nephritis, well outside the transplant setting. [1][3]
4. Trap: Assuming this class's nephrotoxicity is a rare or minor finding.
4. Correction: Historic cyclosporine data recorded nephrotoxicity in roughly a quarter to nearly two-fifths of transplant recipients depending on organ, which is why trough monitoring is mandatory rather than optional. [1]

Self-test questions

1. Question: What is the single mechanistic step that makes cyclosporine and tacrolimus one pharmacological class despite being chemically unrelated?
 1. Both are metabolised by the same hepatic enzyme
 2. Both immunophilin-drug complexes inhibit calcineurin, blocking NFAT-driven interleukin-2 gene transcription
 3. Both bind the same cell-surface cytokine receptor
 4. Both are B-cell-depleting antibodies

1. Explanation: Cyclosporine binds cyclophilin and tacrolimus binds FKBP-12, but both resulting complexes inhibit calcineurin, preventing NFAT dephosphorylation and blocking interleukin-2 transcription - the shared mechanistic endpoint that defines the class. [3]
2. Question: Why can Sandimmune and Neoral cyclosporine not be substituted for each other on a milligram-to-milligram basis?
 1. They are different drugs entirely
 2. Neoral has increased bioavailability compared with Sandimmune, so the two formulations are not bioequivalent
 3. Sandimmune is more potent than Neoral
 4. There is no clinically meaningful difference between them

2. Explanation: The Neoral label states that Neoral has increased bioavailability compared with Sandimmune and that the two are not bioequivalent and cannot be used interchangeably. [1]
3. Question: Which food/drink interaction is specifically flagged for cyclosporine?
 1. Cranberry juice
 2. Grapefruit and grapefruit juice
 3. Orange juice
 4. Green tea

3. Explanation: Grapefruit and grapefruit juice affect cyclosporine metabolism and increase its blood concentration, and the label directs that they should be avoided. [1]
4. Question: New-onset diabetes after transplant is a labelled risk most prominently associated with which calcineurin inhibitor in the material reviewed here?
 1. Cyclosporine
 2. Tacrolimus
 3. Neither drug

4. Both equally, with identical labelled emphasis

4. Explanation: Tacrolimus's label specifically identifies new-onset diabetes after transplant as a risk, with African-American and Hispanic recipients at elevated risk, a labelled emphasis not carried in the same way by cyclosporine's label. [2]

5. Question: Why is therapeutic drug monitoring of trough blood concentrations central to using either calcineurin inhibitor safely?

1. Because it is a regulatory formality with no clinical basis

2. Because the gap between effective immunosuppression and nephrotoxic/neurotoxic levels is narrow for both drugs

3. Because both drugs have no dose-related toxicity at all

4. Because oral absorption of both drugs is always complete and predictable

5. Explanation: Both drugs are dosed against measured whole-blood trough levels precisely because their toxic and effective ranges sit close together, which is what makes fixed dosing without monitoring unsafe. [1][2]

Frequently asked questions

1. Question: Are cyclosporine and tacrolimus basically the same drug?

1. Answer: No. They are structurally unrelated - cyclosporine is a cyclic polypeptide, tacrolimus a macrolide - and bind different immunophilins, cyclophilin and FKBP-12 respectively. What they share is the downstream target, calcineurin, which is why both are called calcineurin inhibitors even though the molecules themselves look nothing alike. [3]

2. Question: Why is grapefruit juice specifically a problem with this class?

2. Answer: It affects cyclosporine's metabolism and raises its blood concentration, and the label directs patients to avoid it. This is a cyclosporine-specific point worth remembering by name rather than a generic rule for every immunosuppressant. [1]

3. Question: Is this class only used after organ transplantation?

3. Answer: No. Cyclosporine also carries its own FDA indications in severe rheumatoid arthritis inadequately responsive to methotrexate and in severe, recalcitrant plaque psoriasis, and calcineurin inhibitors appear in specialist combination regimens for conditions such as lupus nephritis. [1][3]

4. Question: Why do patients on cyclosporine need regular blood tests when other immunosuppressants are monitored less intensively?

4. Answer: Because nephrotoxicity tracks closely with blood concentration, and the gap between an effective dose and a toxic one is narrow. Trough-level monitoring, alongside renal function, is how the dose is kept in the effective range without drifting into the toxic one - it is a routine and expected part of treatment, not a sign that something has gone wrong. [1]

References

[1] NEORAL (cyclosporine) capsules and oral solution - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=94461af3-11f1-4670-95d4-2965b9538ae3>

[2] PROGRAF (tacrolimus) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7f667de1-9dfa-4bd6-8ba0-15ee2d78873b>

[3] Calcineurin Inhibitors. StatPearls Publishing / NCBI Bookshelf 2023. <https://www.ncbi.nlm.nih.gov/books/NBK558995/>

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