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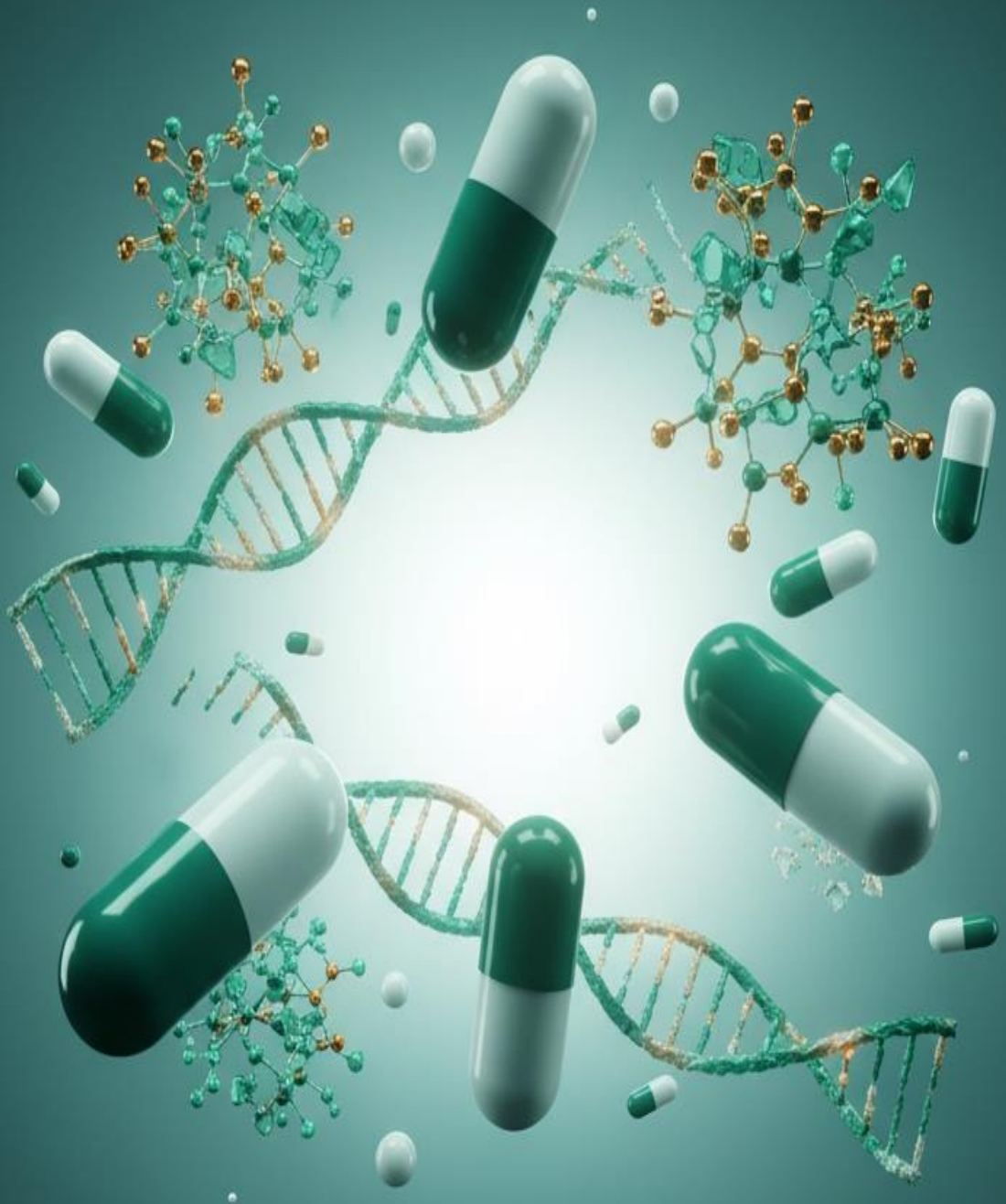

# Immunological and Immunomodulating drugs

2026

# Immunosuppressant Drugs with Clinical Cases

### Definitions by:

CSP | agents that suppress immune function by one of several mechanisms of action; cytotoxic immunosuppressants act by inhibiting DNA synthesis; others may act through activation of suppressor T-cell populations or by inhibiting the activation of helper cells.

MSH | Agents that suppress immune function by one of several mechanisms of action. Classical cytotoxic immunosuppressants act by inhibiting DNA synthesis. Others may act through activation of T-CELLS or by inhibiting the activation of HELPER CELLS. While immunosuppression has been brought about in the past primarily to prevent rejection of transplanted organs, new applications involving mediation of the effects of INTERLEUKINS and other CYTOKINES are emerging.

# Medication Reference Terminology (MED-RT) Classification Hierarchy (2026)

In the MED-RT (Medication Reference Terminology) system—the successor to NDF-RT used by the National Cancer Institute (NCI) and the Department of Veterans Affairs (VA)—immune drugs are classified using a multidimensional hierarchy. It provides a "360-degree" view of a drug by tagging it across four distinct levels: Therapeutic Class [TC], Mechanism of Action [MoA], Physiologic Effect [PE], and Chemical Structure [CS].

### Why MED-RT is Unique

- Multiaxial Definition: A single drug like Methotrexate can be found in multiple trees (e.g., it is both an "Antineoplastic" for cancer and an "Immunosuppressant" for RA).
- Interoperability: MED-RT is designed to help computers and clinical decision systems understand that if a patient is allergic to one "TNF Alpha Blocker," they may have cross-reactivity with others in that same [MoA] category.

> Important
> Data Integration: In 2026, MED-RT remains the "gold standard" for electronic health records (EHR) to ensure that clinicians are alerted to potential drug interactions based on shared Physiologic Effects [PE], even if the drugs belong to different Therapeutic Classes [TC].

> Tip
> When searching for medication information in professional databases, using the [MoA] tag (like "Interleukin Inhibitor") will give you a more accurate list of functional alternatives than searching by broad disease names

As of March 4, 2026, here is the expanded classification for immune-modulating drugs across all major classification systems.

## Therapeutic Class [TC]

*The "Clinical Goal" — What department uses it and for what broad purpose?*

- Antineoplastic and Immunomodulating Agents [TC]
    - Immunosuppressants: To dampen the immune system (Transplants, Autoimmune).
    - Immunostimulants: To boost the immune system (Vaccines, Cancer immunotherapy).
    - Anti-Inflammatory Agents: Specifically focused on the inflammatory cascade.
    - Antirheumatic Agents: Dedicated to bone, joint, and connective tissue.

## Mechanism of Action [MoA]

*The "Biochemical Key" — What specific molecule or receptor does the drug turn on or off?*

Monoclonal Antibody Mechanisms

- Tumor Necrosis Factor (TNF) Alpha Blockers: (e.g., Adalimumab, Infliximab)
- Interleukin (IL) Inhibitors:
    - *IL-6 Inhibitors:* (e.g., Tocilizumab)
    - *IL-17 Inhibitors:* (e.g., Secukinumab)
    - *IL-23 Inhibitors:* (e.g., Risankizumab)
- CD3-Directed Monoclonal Antibodies: (e.g., Teplizumab)
- CD20-Directed Monoclonal Antibodies: (e.g., Rituximab)

Cellular Pathway Mechanisms

- Janus Kinase (JAK) Inhibitors: (e.g., Tofacitinib, Upadacitinib)
- Mechanistic Target of Rapamycin (mTOR) Inhibitors: (e.g., Sirolimus)
- Calcineurin Inhibitors: (e.g., Cyclosporine, Tacrolimus)
- Dihydrofolate Reductase Inhibitors: (e.g., Methotrexate)

Hormonal Mechanisms

- Corticosteroid Hormone Receptor Agonists: (e.g., Prednisone, Dexamethasone)

## Physiologic Effect [PE]

*The "Body Outcome" — What is the visible biological result of taking the drug?*

- Decreased Immune Response: The global result of all immunosuppressants.
- Decreased Inflammatory Response: Specific to drugs that stop cytokine storms.
- T-Lymphocyte Depletion: Specific to CD3 blockers and ATG.
- B-Lymphocyte Depletion: Specific to CD20 blockers like Rituximab.
- Decreased Cell Proliferation: The outcome of antimetabolites and mTOR inhibitors.
- Inhibition of Phagocytosis: The effect of certain steroids on "eater" cells.

## Comprehensive Mapping Table (MED-RT Full View)

This table shows how a single drug is classified across every level of the 2026 MED-RT system.

| Generic Name | Therapeutic Class [TC] | Mechanism [MoA] | Physiologic Effect [PE] |
|---|---|---|---|
| **Methotrexate** | Antineoplastic / DMARD | DHFR Inhibitor | Decreased Cell Proliferation |
| **Adalimumab** | Immunosuppressant | TNF Alpha Blocker | Decreased Inflammatory Response |
| **Sirolimus** | Immunosuppressant | mTOR Inhibitor | Decreased Immune Response |
| **Teplizumab** | Immunosuppressant | CD3-Directed Antibody | T-Lymphocyte Depletion |
| **Rituximab** | Antineoplastic | CD20-Directed Antibody | B-Lymphocyte Depletion |
| **Upadacitinib** | Antirheumatic | Janus Kinase Inhibitor | Decreased Inflammatory Response |
| **Cyclosporine** | Immunosuppressant | Calcineurin Inhibitor | Decreased T-Cell Activation |

## Why "All Classification Systems" Matter

In clinical informatics, this hierarchy allows the medical systems to perform Relationship Mapping:

1. Parent-Child Mapping: Knowing that Adalimumab is a *child* of TNF Alpha Blockers, which is a *child* of Immunosuppressants.
2. Cross-Class Comparison: Identifying that Prednisone and Upadacitinib share the same [PE] (Decreased Inflammatory Response) even though they have completely different [MoA]. NCI Thesaurus

Important
2026 Semantic Integration: The "Chemical Structure" is increasingly used to alert clinicians to drug-drug interactions. For example, if two drugs have different mechanisms but a similar "Sulfonamide" chemical structure, MED-RT will flag a potential allergy risk for the patient.

Tip
When researching a new medication, if the [MoA] is unfamiliar, look at the [PE] (Physiologic Effect). This will tell you the real-world outcome—such as "Decreased Cell Proliferation"—which is often easier to understand than complex protein names.

# Top 50 Immunological and Immunomodulating drugs

The following list represents the Top 50 Immunological and Immunomodulating drugs projected for clinical use and market dominance in 2025–2026. This synthesis includes high-revenue biologics (often used for specialty care)

and high-volume generic immunosuppressants (essential for chronic maintenance). UCB GSK

Comparative numbers are provided as Revenue Projections (in Billions USD) for biologics and Prescription Volume Rank for generic oral medications.

## Part 1: Top 25 High-Revenue Biologics (Market Leaders)

These are the "heavy hitters" of the pharmaceutical world, primarily monoclonal antibodies targeting specific inflammatory cytokines.

| Rank | Brand (Generic) | Primary Class [MoA] | 2025-26 Est. Revenue |
|---|---|---|---|
| **1** | Keytruda (pembrolizumab) | PD-1 Inhibitor (Immunotherapy) | $28.5 B |
| **2** | Dupixent (dupilumab) | IL-4/13 Inhibitor | $15.2 B |
| **3** | Skyrizi (risankizumab) | IL-23 Inhibitor | $12.8 B |
| **4** | Stelara (ustekinumab) | IL-12/23 Inhibitor | $10.5 B |
| **5** | Opdivo (nivolumab) | PD-1 Inhibitor | $9.8 B |
| **6** | Humira (adalimumab) | TNF Inhibitor | $8.2 B (declining) |
| **7** | Biktarvy (bictegravir/+) | Anti-Retroviral (Immune focus) | $7.9 B |
| **8** | Rinvoq (upadacitinib) | JAK Inhibitor | $7.2 B |
| **9** | Enbrel (etanercept) | TNF Inhibitor | $6.5 B |
| **10** | Cosentyx (secukinumab) | IL-17A Inhibitor | $5.9 B |
| **11** | Ocrevus (ocrelizumab) | CD20-Directed (MS focus) | $5.4 B |
| **12** | Tremfya (guselkumab) | IL-23 Inhibitor | $4.8 B |
| **13** | Entyvio (vedolizumab) | Integrin Receptor Antagonist | $4.5 B |
| **14** | Darzalex (daratumumab) | CD38-Directed | $4.2 B |
| **15** | Xolair (omalizumab) | Anti-IgE | $3.9 B |
| **16** | Otezla (apremilast) | PDE4 Inhibitor | $3.5 B |
| **17** | Taltz (ixekizumab) | IL-17A Inhibitor | $3.2 B |
| **18** | Nucala (mepolizumab) | IL-5 Inhibitor | $2.8 B |
| **19** | Simponi (golimumab) | TNF Inhibitor | $2.5 B |
| **20** | Actemra (tocilizumab) | IL-6 Inhibitor | $2.2 B |
| **21** | Orencia (abatacept) | T-cell Costimulation Blocker | $2.1 B |
| **22** | Benlysta (belimumab) | BLyS-Specific Inhibitor | $1.9 B |
| **23** | Fasenra (benralizumab) | IL-5 Receptor Antagonist | $1.8 B |
| **24** | Tezspire (tezepelumab) | TSLP Inhibitor | $1.6 B |
| **25** | Kesimpta (ofatumumab) | CD20-Directed | $1.5 B |

## Part 2: Top 25 High-Volume Generic Immunosuppressants

While these generate less revenue due to low cost, they account for the vast majority of prescriptions written globally for immune health. Business Research Co

| Volume Rank | Generic Name | Common Use | Clinical Significance |
|---|---|---|---|
| **26** | Prednisone | Widespread | #1 Most Prescribed global steroid. |
| **27** | Methotrexate | RA / Psoriasis | "Gold standard" anchor for DMARD therapy. |
| **28** | Hydroxychloroquine | Lupus / RA | Essential for flare prevention. |
| **29** | Tacrolimus | Transplants | Critical for organ rejection prevention. |
| **30** | Azathioprine | IBD / Systemic | Broad systemic immunosuppressant. |
| **31** | Cyclosporine | Dry Eye / Transplants | Calcineurin inhibitor standard. |
| **32** | Mycophenolate Mofetil | Lupus Nephritis | Primary steroid-sparing agent. |
| **33** | Leflunomide | RA | Oral alternative to Methotrexate. |
| **34** | Sulfasalazine | IBD / RA | Older, reliable sulfa-based DMARD. |
| **35** | Dexamethasone | Acute Crisis | High-potency emergency steroid. |
| **36** | Sirolimus | Transplants | Standard mTOR inhibitor. |
| **37** | Everolimus | Post-Transplant | Second-line mTOR maintenance. |
| **38** | Cyclophosphamide | Severe Organ Attack | Cytotoxic agent for critical cases. |
| **39** | Montelukast | Allergy/Asthma | Most prescribed leukotriene modifier. |
| **40** | Fluticasone | Asthma/Allergy | Highest volume inhaled/nasal steroid. |
| **41** | Budesonide | Crohn's/Asthma | Locally active corticosteroid. |
| **42** | Mesalamine | Ulcerative Colitis | Primary 5-ASA for gut health. |
| **43** | Colchicine | Gout / Pericarditis | Specific anti-inflammatory. |
| **44** | Dapsone | Polychondritis | Specific for cartilage/skin issues. |
| **45** | IVIG (Immune Globulin) | PID / Neurological | Essential antibody replacement. |
| **46** | Rituximab Biosimilars | Lymphoma / RA | High-use B-cell depleter. |
| **47** | Infliximab Biosimilars | IBD / AS | Cost-effective TNF therapy. |
| **48** | Adalimumab Biosimilars | RA / Psoriasis | Massive uptake in 2025–26. |
| **49** | Tofacitinib | RA / UC | First-generation oral JAK inhibitor. |
| **50** | Upadacitinib | Dermatitis / RA | Rapidly rising oral synthetic DMARD. |

## Key Market Trends for 2026

- The "Erosion" of Humira: Once the #1 drug in history, Humira continues its revenue decline in 2026 as low-cost biosimilars take over the market. Persistence Market Research
- The Rise of JAKs: Oral pills like Rinvoq and Xeljanz are capturing significant share from injectable biologics, particularly in patients with moderate-to-severe IBD and Atopic Dermatitis.
- Precision Cytokine Targeting: Notice that Skyrizi and Dupixent are now out-earning older "broad" biologics like Enbrel. This reflects a shift toward medicines that only block one specific protein (like IL-23) rather than a broad family (like TNF).

Important
Prescription Disparity: Although Keytruda is Rank #1 in revenue, a primary care doctor might prescribe Prednisone 1,000 times for every 1 time they see a patient on Keytruda. Revenue numbers reflect the high cost of biological manufacturing rather than the number of people taking the drug.

Tip
In 2026, many insurance plans now mandate "Step Therapy"—requiring patients to try Rank 27 (Methotrexate) before they will cover Rank 3 (Skyrizi). UHC

# Understand the landscape of immunological drugs.
# Streamline knowledge about immunosuppressive drugs.

Today, we're going to simplify immunosuppressant drugs.
These medications reduce the immune system's activity.
But why would we want to weaken the immune system?
Two main reasons:

1. To prevent organ transplant rejection.
2. To treat autoimmune diseases, where the immune system attacks the body.

Let's break this down step by step.
To understand the landscape of immunological drugs in 2026, it is best to group them by their "biological target." While many of these drugs treat the same diseases (like Rheumatoid Arthritis or Psoriasis), how they attack the inflammation is what defines their group and their differences.

## Group 1: The "Master Switch" (TNF-Alpha Inhibitors)

These were the first generation of biologics. They block Tumor Necrosis Factor (TNF), a protein that acts as a "master switch" for inflammation.

- Humira (adalimumab): The most famous of the group. It is a fully human antibody, used for a wide range of conditions (RA, Crohn's, Psoriasis).
- Enbrel (etanercept): Difference: Unlike Humira, this is a "fusion protein" rather than a monoclonal antibody. It typically stays in the body for a shorter time and is often preferred for patients who may need to stop treatment quickly (e.g., for surgery).
- Remicade (infliximab): Difference: This must be given as an IV infusion in a clinic, whereas Humira and Enbrel are self-injections at home. It works faster for severe gut inflammation (Crohn's).

## Group 2: The "Precision Snipers" (Interleukin Inhibitors)

Instead of turning off a "master switch," these target very specific proteins (Interleukins) involved in specific diseases.

- Skyrizi (risankizumab) & Tremfya (guselkumab): Target IL-23.
  - The Power: These are the most effective drugs for Skin Psoriasis in 2026, often achieving 100% clear skin.
- Dupixent (dupilumab): Targets IL-4 and IL-13.
  - Difference: It is unique because it treats "Type 2" inflammation, making it the gold standard for Atopic Dermatitis (Eczema) and Asthma, rather than joint-focused diseases.
- Cosentyx (secukinumab) & Taltz (ixekizumab): Target IL-17A.
  - Difference: These are the preferred choice for Ankylosing Spondylitis because IL-17 is the primary driver of spinal fusion.

## Group 3: The "Oral Messengers" (JAK Inhibitors)

Unlike biologics (which are large proteins that must be injected), these are small molecules that can be taken as pills.

- Xeljanz (tofacitinib): The first of its kind. It blocks multiple JAK pathways.
- Rinvoq (upadacitinib): Difference: It is a "Selective" JAK-1 inhibitor. By only blocking JAK-1, it aims to be more potent for conditions like RA and Eczema while potentially reducing some of the blood-related side effects seen with older JAK inhibitors.

## Group 4: The "Foundation" (Traditional DMARDs)

These are older, low-cost drugs that remain the first line of defense for almost all patients, serve as the "anchor" for treating chronic inflammation and preventing organ rejection. Traditional DMARDs (also known as csDMARDs or "conventional synthetic" DMARDs) are the long-standing, pill-based medications used to slow the progression of autoimmune diseases. Unlike biologics, which are made in living cells, these are chemically synthesized.

### 4.1 The DNA Blockers (Antimetabolites)

This sub-group works inside the cell to stop the production of DNA building blocks. If immune cells cannot make DNA, they cannot divide and attack.

How They Work

- Mechanism [MoA]: These drugs act as Nucleotide Synthesis Inhibitors. They mimic the natural molecules (metabolites) that the body uses to build DNA.
- Physiologic Effect [PE]: Decreased Cell Proliferation. When an immune cell tries to divide to attack a joint or a transplanted organ, it accidentally uses the drug instead of real DNA building blocks. This "breaks" the copying process, and the cell cannot multiply.

Common Examples

- Trexall (methotrexate): The primary "anchor" drug for Rheumatoid Arthritis.
- Imuran (azathioprine): Frequently used for Crohn's Disease and Lupus.
- CellCept (mycophenolate mofetil): A standard for preventing rejection in kidney and liver transplants.

> Important
> Safety Priority: Because these drugs stop cells from dividing, they can affect the bone marrow. Regular blood counts (CBC) are mandatory to monitor for Leukopenia (low white blood cells).

### Clinical Case: The Risk of Over-Suppression

The Scenario: A patient with Rheumatoid Arthritis has been successfully managing their pain with Methotrexate for several months. However, a routine blood test suddenly shows a dangerously low white blood cell count (Leukopenia).

The Explanation: Because antimetabolites stop cells from dividing, they don't just affect "bad" immune cells; they can also affect "good" cells in the bone marrow where all blood cells are born. This is known as Bone Marrow Suppression (or Myelosuppression).

> Important
> Monitoring is Mandatory: Because of the risk of bone marrow suppression, patients on antimetabolites must have regular Complete Blood Count (CBC) and Liver Function Tests (LFTs). If counts drop too low, the drug must be paused to allow the marrow to recover.

> Tip
> To reduce the "DNA-breaking" side effects on healthy cells, patients taking Methotrexate are almost always prescribed Folic Acid (Vitamin B9). Taking folic acid on the days you *don't* take your methotrexate helps protect your mouth, hair, and blood cells without stopping the drug from working on your arthritis.

### 4.2 Cellular Modulators

These drugs do not stop cell division. Instead, they "calm" the immune system by interfering with how cells communicate or by blocking specific non-DNA pathways. These drugs are still "Disease-Modifying," but they do not work by blocking DNA synthesis. Instead, they change the pH of cells, block specific enzymes, or reduce inflammation through signaling. Key Drugs:

- Plaquenil (hydroxychloroquine),
- Azulfidine (sulfasalazine),
- Arava(leflunomide).

Comparison: Antimetabolites vs. Modulators

| Feature | DNA Blockers (Antimetabolites) | Cellular Modulators |
|---|---|---|
| Action | Suppresses (Stops growth) | Modulates (Calms) |
| Infection Risk | High | Low to None |
| Marrow Risk | Significant (Requires CBC) | Minimal |
| Primary Risk | Liver / Lung / Marrow | Eyes (for HCQ) / BP (for Arava) |

These are high-volume, cost-effective medications that serve as the "anchor" for treating chronic inflammation and preventing organ rejection.

## Plaquenil(hydroxychloroquine)

is considered a Traditional DMARD (Disease-Modifying Anti-Rheumatic Drug). However, it is distinct from others in its class because it does not act as an "immunosuppressant" in the classic sense—it is an Immunomodulator.

- The "Calmer": Originally an antimalarial; now the foundation for Lupus (SLE) and mild RA.
- Mechanism: Immunomodulator that interferes with antigen presentation.
- Key Monitoring: Annual specialized eye exams (retinal check).

## Azulfidine(sulfasalazine)

- The "Double Action": A combination of a salicylate (anti-inflammatory) and a sulfa antibiotic.
- Use: Common for RA, Ulcerative Colitis, and Ankylosing Spondylitis.
- Key Monitoring: Blood counts and liver function.

While Methotrexate is like a "fire extinguisher" that puts out the flames by stopping cell growth, Hydroxychloroquine is like a "thermostat" that turns down the heat of the immune system.

Why it is Different (The "Calming" Effect)

1. Mechanism [MoA]: It was originally an antimalarial drug. In autoimmune disease, it works by interfering with antigen presentation and changing the pH inside immune cells. This prevents the immune system from getting "over-excited" by the body's own DNA.
2. Safety Profile: Unlike Methotrexate or Biologics, Plaquenil does not increase the risk of serious infections or cancer. This is why it is often the first drug prescribed for mild-to-moderate disease.
3. Lupus "Life Insurance": For patients with Systemic Lupus Erythematosus (SLE), Plaquenil is considered mandatory "life insurance." It is the only drug proven to prevent long-term damage to the kidneys and heart and to extend the lifespan of Lupus patients.

*Comparison: Plaquenil vs. Methotrexate*

| Feature | Plaquenil (hydroxychloroquine) | Trexall (methotrexate) |
|---|---|---|
| Category | Traditional DMARD (Antimalarial) | Traditional DMARD (Antimetabolite) |
| Action | Modulates (Calms) | Suppresses (Stops growth) |
| Infection Risk | No significant increase | Increased risk |
| Monitoring | Yearly Eye Exams | Monthly Blood Work (CBC/Liver) |
| Best For | Lupus, mild RA, Sjögren's | Moderate-to-severe RA, Psoriasis |

Important

The Eye Check: While Plaquenil is very safe for the blood and liver, its major long-term risk is Retinal Toxicity (damage to the back of the eye). Patients on this drug must have a specialized eye exam (Visual Field and OCT) once a year to ensure the drug isn't building up in the retina.

Important

Combination Therapy: It is very common for patients to be on a "triple therapy" combination of these drugs (usually Methotrexate + Hydroxychloroquine + Sulfasalazine). This is often as effective as a biologic for many patients but at a much lower cost.

Tip

Traditional DMARDs do not work immediately. It typically takes 6 to 12 weeks of consistent use before a patient feels the full therapeutic benefit. This is why doctors often use "Bridge Therapy" with steroids during the first few months.

## Group 5: The "Emergency Responders" (Corticosteroids)

- Prednisone
- Methylprednisolone
- Dexamethasone

1. "Work at the gene level"
Unlike biologics (which work *outside* the cell by soaking up proteins), corticosteroids are lipophilic. They pass directly through the cell membrane and bind to receptors in the cytoplasm. This receptor-drug complex then moves into the nucleus of the cell, where it binds to DNA to "turn off" or "turn on" specific genes. This is the definition of a Genomic Effect.
2. "Reduce cytokines like IL-1, IL-2, and TNF"
Once inside the nucleus, steroids block the transcription of pro-inflammatory genes.

- IL-1 & TNF: These are the primary "drivers" of inflammation. Steroids inhibit the master switch (NF-κB) that usually tells the cell to produce these cytokines.
- IL-2: This is the "growth fuel" for T-cells. By reducing IL-2 at the genetic level, steroids prevent the immune system from multiplying its "soldier" cells. NCBI

Think of steroids as the master “off switch” for inflammation. These work almost instantly to shut down all immune activity. Difference: Dexamethasone is much more potent (about 25 times stronger than hydrocortisone) and is reserved for acute crises or brain swelling, whereas Prednisone is the standard for daily tapering in RA or PMR.

It is important not to confuse this with other classes that target the same cytokines but in different ways:

| Drug Class | How it reduces cytokines | Location of Action |
|---|---|---|
| Corticosteroids | Stops the production by editing gene transcription. | Inside the Nucleus |
| JAK Inhibitors | Blocks the signal sent by the cytokine after it's made. | Inside the Cytoplasm |
| Biologics (TNF-i) | Neutralizes the protein after it's released into the blood. | Outside the Cell |

> Important
> Because steroids work at the gene level across almost all cell types, they have widespread side effects (like bone thinning or weight gain). This is why modern medicine tries to use "Precision" drugs (like Biologics) that only target one cytokine rather than stopping the genetic production of many at once.

> Tip
> In your ebook, you can use this sentence as the opening line for Group 5: The Emergency Responders (Corticosteroids) to explain their broad, powerful, and fundamental impact on the immune system.

### Clinical Case Example:

A 32-year-old woman with lupus presents with severe joint pain and kidney inflammation.
She is started on high-dose intravenous methylprednisolone.
Why?
Because steroids act quickly to calm an aggressive immune flare.
Key Side Effects:
Hyperglycemia, Weight gain, Osteoporosis, Increased infection risk
Important Reminder:
Steroids are powerful — but long-term use causes systemic side effects.

## Group 6: Cell Depleters (B-Cell & T-Cell Directed) & Targeted Biologics

These advanced therapies represent the "precision" era of immunology. Unlike older drugs that dampen the entire system, these agents are engineered to target specific surface markers or receptors on individual immune cells.

### B-Cell Directed Therapy

B-cells (B-lymphocytes) are white blood cells that produce antibodies. While essential for fighting germs, in autoimmune disease, they can produce "autoantibodies" that attack the body.

#### Rituxan (rituximab):

- Mechanism [MoA]: CD20-Directed Monoclonal Antibody.
- Physiological Effect [PE]: B-Lymphocyte Depletion.
- Clinical Use: By "wiping out" the B-cell population for 6 to 12 months, it provides a deep reset for patients with Non-Hodgkin Lymphoma or severe Rheumatoid Arthritis.

### T-Cell Directed & Receptor Blockers

T-cells are the "conductors" of the immune response. These drugs prevent T-cells from attacking tissues or receiving the signals they need to activate.

#### Tzield (teplizumab):

- Difference: This is a CD3-directed T-cell blocker. It is the first and only drug approved to delay the clinical onset of Type 1 Diabetes. It works by "shielding" the insulin-producing cells in the pancreas from T-cell destruction.

#### Simulect (basiliximab):

- Mechanism [MoA]: IL-2 Receptor Antagonist.
- Clinical Use: Specifically prevents T-cells from activating immediately after an organ transplant, reducing the risk of acute rejection.

#### Nulojix (belatacept):

- Mechanism [MoA]: T-cell Costimulation Blocker.
- Difference: It blocks the specific "handshake" (signals CD80 and CD86) required for a T-cell to recognize a foreign organ. It is often used as a long-term, kidney-friendly alternative to cyclosporine. PMC

### Clinical Case: Moving to Precision Care

The Scenario: A 45-year-old patient with severe Rheumatoid Arthritis has seen no improvement after six months of high-dose Methotrexate. Transition: Because her disease is driven by autoantibodies, her rheumatologist escalates her therapy to Rituxan (rituximab) to clear the B-cells responsible for the attack.

> Important
> Safety Protocol: Before starting any "Cell Depleter," patients must be screened for Hepatitis B. Because these drugs effectively remove a portion of the immune "security detail," latent viruses like Hep B can reactivate and cause severe liver damage if not identified beforehand.

> Tip
> While these drugs are more powerful than traditional immunosuppressants, they are also more targeted. This means that while you may have a higher risk of specific infections, you avoid the widespread, "shotgun" side effects (like bone loss or hair thinning) common with older, broad-spectrum drugs.

## Group 7: The "Growth Blockers" (mTOR & Calcineurin Inhibitors)

Primarily used in Transplant Medicine to prevent the body from rejecting a new organ.

### Calcineurin Inhibitors

- Cyclosporine
- Tacrolimus

Prograf( tacrolimus): A calcineurin inhibitor. It is the "anchor" drug for kidney and liver transplants.
These drugs block calcineurin, preventing Interleukin-2 production.
No Interleukin-2 means no T-cell activation.
T-cells (T lymphocytes) are critical white blood cells of the adaptive immune system that originate in the bone marrow and mature in the thymus. They destroy infected or cancerous cells, regulate immune responses, and create memory cells for long-term immunity.
These are cornerstone drugs in transplant medicine.

### *Clinical Case Example:*

A 55-year-old man receives a kidney transplant.
He is started on tacrolimus for long-term rejection prevention.
Two months later, his creatinine begins to rise.
What is the concern?
Nephrotoxicity — the most important side effect of calcineurin inhibitors.
Key Takeaway:
When you think CNIs (Calcineurin Inhibitors), think: T cells… and kidneys.

### Target of Rapamycin (mTOR) Inhibitors

- Sirolimus
- Everolimus

Difference: An mTOR inhibitor. While Tacrolimus stops T-cell *activation*, Sirolimus stops the T-cells from *multiplying* after they've been activated. It is often used if a patient cannot tolerate the kidney-related side effects of Tacrolimus.
These drugs block the mTOR pathway.
That stops T-cell proliferation — meaning immune cells cannot multiply.
They are sometimes used as alternatives to calcineurin inhibitors.

### Clinical Case Example:

A transplant patient develops worsening kidney function on tacrolimus.
The physician switches to sirolimus.
Why?
Because mTOR inhibitors cause less kidney toxicity.
However, the patient later develops high cholesterol and delayed wound healing — known side effects of this class.

> Important
> The 2026 Trend: The most significant difference between these groups is that medicine is moving away from Group 5 (Steroids) and Group 1 (Broad TNF blockers) toward Group 2 (Precision Interleukins). This "narrow targeting" allows for better disease control with fewer systemic side effects like weight gain or bone loss.

> Tip
> If a patient is failing a drug in Group 1, a doctor will often switch them to a different Group (like Group 2 or 3) rather than another drug in the same family. This is called "switching the mechanism."

# Closing Summary

Let’s review:

- **Steroids** — broad suppression
- **Calcineurin inhibitors** — block T-cell activation
- **mTOR inhibitors** — block cell growth
- **Antimetabolites** — block DNA synthesis
- **Biologics** — targeted immune blocking

**Universal Rule:**
If you suppress the immune system, **infection risk increases**.

Understanding this principle helps predict side effects and guide clinical decisions.

And that’s the foundation of immunosuppressant therapy.

# Cyclophosphamide

## Is this a chemotherapy or immunotherapy drug?

Cyclophosphamide is primarily an alkylating chemotherapy drug used to treat various cancers (lymphoma, breast, ovarian) by damaging DNA to kill cancer cells. However, at low doses, it acts as an immunomodulator by reducing regulatory T cells, which helps boost the immune system's attack on tumors.

- Chemotherapy (High Dose): Acts as a traditional cytotoxic agent that kills rapidly dividing cells.
- Application: Given intravenously or orally for cancer treatment, and also used as an immunosuppressant for autoimmune diseases.
- Autoimmune Diseases: Used for severe lupus (SLE), systemic sclerosis, vasculitis, and dermatomyositis.
- Organ Transplant: Sometimes used in transplantation.
- Other Conditions: Used for severe nephrotic syndrome.
- Immunotherapy (Low Dose/Metronomic): Used to "repurpose" the immune system, making it a common partner for immunotherapy drugs (like checkpoint inhibitors) to make tumors more visible to the immune system

It works by killing or slowing the growth of rapidly dividing cells, including immune cells (T and B cells) responsible for inflammation and autoimmune diseases.

Cyclophosphamide is an alkylating chemotherapy agent with dose-dependent immunologic effects. It is not a true immunotherapy.

**Drug Class**

- **Alkylating agent (nitrogen mustard)**
- Cell cycle–nonspecific
- Causes **DNA cross-linking → apoptosis**

## High Dose = Chemotherapy / Immunosuppression

At standard or high doses, cyclophosphamide acts as a **cytotoxic chemotherapy drug**.

**Mechanism:**

- Kills rapidly dividing cells
- Affects:
  - Cancer cells
  - Immune cells (T and B lymphocytes)

## Clinical uses

Malignancies:

- Lymphoma
- Breast cancer
- Ovarian cancer

Severe autoimmune disease:

- SLE (especially lupus nephritis)
- Vasculitis
- Systemic sclerosis
- Dermatomyositis

Other:

- Severe nephrotic syndrome
- Ocasionally organ transplantation

**Key concept:**
High-dose cyclophosphamide = **broad immunosuppression**

**Low Dose / Metronomic = Immunomodulation**

At **low or metronomic doses**, cyclophosphamide has **selective immune effects**.

**Mechanism:**

- Preferential depletion of **regulatory T cells (Tregs)**
- Enhances antitumor immune responses

**Clinical implication:**

- Used as an **adjunct** to immune checkpoint inhibitors
- Helps make tumors more immunogenic

**Important distinction:**

- This is **immunomodulation, not immunotherapy**
- It does **not** directly activate immune checkpoints or target immune receptors

# Methotrexate

Dihydrofolate reductase (DHFR) inhibitors, a class of medications that block the DHFR enzyme, preventing the conversion of dihydrofolate to active tetrahydrofolate, which is essential for DNA synthesis and cell division. These antifolates are used to treat cancer, autoimmune diseases, and bacterial/protozoal infections.

**Methotrexate is ALWAYS an antimetabolite (DHFR inhibitor).**
Whether it's called "chemotherapy" or "immunosuppressant" depends on the **dose and indication**, not the drug class.

**1. Chemotherapy (High Dose)**

**Class:** Antimetabolite chemotherapy
**Use:** Cancer treatment
- (e.g., leukemia, lymphoma, osteosarcoma)

**Effect:** Cytotoxic to rapidly dividing cells
**Toxicities:** Myelosuppression, mucositis
**Rescue: Leucovorin (folinic acid)**

**2. Immunosuppressant / Immunomodulator (Low Dose)**

**Class:** Antimetabolite immunosuppressant
**Use:** Autoimmune diseases
- Rheumatoid arthritis
- Psoriasis
- Inflammatory bowel disease

**Effect:** ↓ lymphocyte proliferation

# Immunosuppresant Drugs Table

| Drug | Drug Class | Primary Immune Target | Typical Clinical Use (Exam-Relevant) |
|---|---|---|---|
| **Prednisone** | Corticosteroid | ↓ Cytokine transcription (IL-1, IL-2, TNF-α) | Autoimmune disease, transplant rejection, acute immune flares |
| **Methylprednisolone** | Corticosteroid | Broad suppression of innate & adaptive immunity | Severe autoimmune disease, transplant rejection |
| **Dexamethasone** | Corticosteroid | Potent anti-inflammatory, ↓ cytokines | Autoimmune disease, inflammation control |
| **Cyclosporine** | Calcineurin inhibitor | ↓ IL-2 → ↓ T-cell activation | Organ transplantation, autoimmune disease |
| **Tacrolimus** | Calcineurin inhibitor | ↓ IL-2 → ↓ T-cell activation | Organ transplantation (cornerstone drug) |
| **Sirolimus** | mTOR inhibitor | ↓ T-cell proliferation (cell cycle arrest) | Transplant patients with CNI nephrotoxicity |
| **Everolimus** | mTOR inhibitor | ↓ T-cell proliferation | Transplant maintenance |
| **Azathioprine** | Antimetabolite | ↓ Purine synthesis → ↓ lymphocyte proliferation | Transplant maintenance, autoimmune disease |
| **Mycophenolate mofetil** | Antimetabolite | ↓ Guanine synthesis (lymphocyte-specific) | Transplant maintenance, autoimmune disease |
| **Methotrexate (low dose)** | Antimetabolite (DHFR inhibitor) | ↓ DNA synthesis → ↓ lymphocyte proliferation | Rheumatoid arthritis, psoriasis, IBD |
| **Rituximab** | Biologic (anti-CD20) | B-cell depletion | Autoimmune disease, transplant-related immune control |
| **Basiliximab** | Biologic (IL-2 receptor blocker) | Blocks T-cell activation | Transplant rejection prevention |
| **Belatacept** | Biologic (costimulation blocker) | Blocks CD80/86 → ↓ T-cell activation | Kidney transplantation |
| **Cyclophosphamide** | Alkylating agent (dose-dependent) | DNA cross-linking → lymphocyte death | Severe autoimmune disease (SLE, vasculitis); immunosuppressive at high dose |