

Conventional DMARDs

The oldest disease-modifying antirheumatic drugs - methotrexate, hydroxychloroquine, sulfasalazine and leflunomide - grouped only by being small synthetic molecules rather than by a shared mechanism, and unified in practice by mandatory laboratory monitoring rather than by how each one actually works.

Online guide: <https://www.medguideglobal.com/pharmacology/immunomodulators/conventional-dmards>

Content updated: 2026-08-24

Quick revision

One Liner: Four drugs held together by history and by the label "first tried," not by one mechanism: an antifolate, a 4-aminoquinoline, a 5-ASA-linked sulfonamide, and a pyrimidine-synthesis inhibitor - each with its own toxicity and its own monitoring schedule.

1. Methotrexate for rheumatoid arthritis is dosed WEEKLY, not daily - mistaken daily dosing has caused fatal toxicity, and every prescriber and pharmacist is directed to say so out loud. [1]
2. Methotrexate inhibits dihydrofolate reductase, blocking DNA synthesis in rapidly dividing cells, which is also why it is contraindicated in pregnancy and in alcoholic or chronic liver disease. [1]
3. Hydroxychloroquine's dose-related retinal toxicity can progress even after the drug is stopped, which is exactly why it is screened for rather than waited for. [2]
4. Sulfasalazine carries its own contraindication most of this class does not: true sulfonamide or salicylate hypersensitivity, because the molecule is built from both. [3]
5. Leflunomide's boxed warning is a pair - teratogenicity and hepatotoxicity - and because its active metabolite recirculates enterohepatically for months, stopping the drug alone does not clear it from the body. [4]
6. Leflunomide requires a distinct accelerated drug-elimination procedure with cholestyramine or activated charcoal, confirmed by two plasma levels 14 or more days apart, precisely because ordinary discontinuation is not enough. [4]
7. Modern classification calls this group conventional synthetic DMARDs (csDMARDs) specifically to separate it from the biologic and targeted synthetic agents that came later and act on a single defined molecular target. [5]
8. Combining a conventional DMARD with a biologic DMARD is standard practice; combining two biologics, or a biologic with a JAK inhibitor, is not. [5]

Overview

1. "Conventional DMARD" is a category invented in hindsight. Methotrexate, hydroxychloroquine, sulfasalazine and leflunomide were not designed as a family - one is an antifolate developed for cancer, one is an antimalarial repurposed for autoimmune disease, one is a sulfonamide-salicylate hybrid built for ulcerative colitis, and one is a purpose-built pyrimidine-synthesis inhibitor. Modern classification calls them conventional synthetic DMARDs (csDMARDs) specifically to distinguish them from the biologic DMARDs and the targeted synthetic DMARDs (JAK inhibitors) that followed, both of which act on one defined molecular target rather than several diffuse ones. [5]
2. What actually unites the group in practice is not mechanism but monitoring. Methotrexate needs baseline and ongoing blood counts, liver enzymes, renal function and a chest X-ray; leflunomide needs monthly ALT and blood counts for six months and then every six to eight weeks; sulfasalazine needs blood counts and liver function on a biweekly-then-monthly-then-quarterly schedule; hydroxychloroquine needs baseline and then annual retinal screening after five years of use. None of that monitoring is optional housekeeping - it is how marrow, hepatic and pulmonary toxicity are caught before they become irreversible. [1][4][3][2]
3. Two members of the class carry reproductive warnings serious enough to shape the whole prescription. Methotrexate is contraindicated in pregnancy and causes fetal death or congenital anomalies; leflunomide's boxed

warning pairs that same teratogenicity with a metabolite so persistent that stopping the tablets is not enough to clear it, which is why an accelerated elimination procedure exists at all. Hydroxychloroquine is the exception rather than the rule here: decades of use in pregnant patients with lupus and malaria have not shown the same signal. [1][4][2]
 4. Onset is slow across the class - weeks to a few months rather than days - which is the pharmacological reason these drugs are called disease-modifying rather than simply anti-inflammatory. A patient and prescriber judging effect too early is one of the most common practical errors made with this group. [5]

Classification and drug examples

Intro: Grouped here by the mechanism each drug actually uses, since the four have almost nothing chemically in common beyond predating the biologic era.

1. Name: Antifolate (dihydrofolate reductase inhibitor)

1. Note: A single drug, methotrexate, used at a low weekly dose in rheumatic disease - pharmacologically distinct from the high daily antineoplastic doses used in cancer.

Name: Methotrexate

1. Trexall

2. Rheumatrex

Route: Oral or subcutaneous, once weekly

Note: Anchor drug of rheumatoid arthritis therapy; the label requires the prescriber and pharmacist to both emphasise the weekly schedule to the patient. [1] [1]

2. Name: 4-Aminoquinoline antimalarial

2. Note: Repurposed from malaria treatment; its anti-inflammatory mechanism in rheumatic disease is not fully established.

Name: Hydroxychloroquine

Plaquenil

Route: Oral

Note: The mildest agent in this class by marrow and hepatic toxicity, but the one most defined by a cumulative, potentially irreversible retinal risk. [2] [2]

3. Name: Sulfonamide-salicylate hybrid

3. Note: Split in the body into sulfapyridine and 5-aminosalicylic acid; the anti-inflammatory and immunomodulatory effect is attributed to the combination rather than to one fragment alone.

Name: Sulfasalazine

Azulfidine

Route: Oral

Note: Carries a true sulfonamide/salicylate hypersensitivity contraindication that the rest of this class does not share. [3] [3]

4. Name: Pyrimidine synthesis inhibitor

4. Note: Blocks dihydroorotate dehydrogenase, starving rapidly dividing lymphocytes of pyrimidines needed for proliferation.

Name: Leflunomide

Arava

Route: Oral

Note: The only member of this class with a two-part boxed warning and a dedicated drug-elimination procedure for its long-lived active metabolite. [4] [4]

Mechanism of action

Summary: There is no single mechanism here. Methotrexate starves DNA synthesis by blocking dihydrofolate reductase; leflunomide starves it a different way, by blocking pyrimidine synthesis at dihydroorotate dehydrogenase;

sulfasalazine acts through anti-inflammatory and immunomodulatory properties whose full basis is still being worked out; and hydroxychloroquine's anti-rheumatic mechanism remains incompletely understood even though its antimalarial action - concentrating in parasite acid vesicles and inhibiting heme polymerisation - is well characterised. What the class shares is an onset measured in weeks, not days.

Target: Four distinct targets: dihydrofolate reductase (methotrexate), dihydroorotate dehydrogenase (leflunomide), an incompletely defined anti-inflammatory pathway (sulfasalazine), and lysosomal/acid-vesicle function relevant to its antimalarial action (hydroxychloroquine)

Cidal Static: Disease-modifying rather than curative - inflammation and joint damage are slowed or halted, not eliminated

Kill Kinetics: Delayed onset over weeks to a few months; effect requires sustained dosing and is lost on stopping

1. Step: 1

1. Title: Methotrexate blocks dihydrofolate reductase

1. Detail: It inhibits the enzyme, interfering with DNA synthesis, repair and cellular replication in rapidly proliferating tissue - the same mechanism used at far higher doses in cancer chemotherapy. [1]

2. Step: 2

2. Title: Leflunomide blocks a different, pyrimidine-based route to the same end

2. Detail: Its active metabolite inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme in de novo pyrimidine synthesis, producing antiproliferative and anti-inflammatory effects in activated lymphocytes. [4]

3. Step: 3

3. Title: Sulfasalazine is split in the gut into two active fragments

3. Detail: Gut bacteria cleave it into sulfapyridine and 5-aminosalicylic acid; the drug's anti-inflammatory and immunomodulatory effect, and its affinity for connective tissue and serous fluid, are attributed to the combination rather than to either fragment alone. [3]

4. Step: 4

4. Title: Hydroxychloroquine's antimalarial mechanism is well defined; its anti-rheumatic one is not

4. Detail: As a 4-aminoquinoline it concentrates in parasite acid vesicles and inhibits haem polymerisation in malaria. Its benefit in rheumatoid arthritis and lupus is real and reproducible, but the underlying anti-inflammatory mechanism remains incompletely understood. [2]

5. Step: 5

5. Title: All four require weeks to show clinical effect

5. Detail: Because none of these mechanisms acts on an acute inflammatory mediator directly, disease control builds gradually - this is the pharmacological basis for describing the class as disease-modifying rather than symptom-relieving. [5]

Major clinical uses

1. Drug: Methotrexate

1. Organism: Not applicable

1. Indication: Active rheumatoid arthritis, once-weekly dosing

1. Line: first-line anchor drug

1. Note: The label directs both prescriber and pharmacist to emphasise the weekly schedule; mistaken daily use of the recommended dose has led to fatal toxicity. [1]

2. Drug: Hydroxychloroquine

2. Organism: Not applicable

2. Indication: Rheumatoid arthritis, systemic lupus erythematosus, chronic discoid lupus erythematosus

2. Line: first-line, often combined

2. Note: Also indicated for malaria treatment and prophylaxis in chloroquine-sensitive areas - a reminder of its origin outside rheumatology. [2]

- 3. Drug: Sulfasalazine
- 3. Organism: Not applicable
- 3. Indication: Rheumatoid arthritis; mild to moderate ulcerative colitis and maintenance of remission
- 3. Line: first-line for RA, standard for UC
- 3. Note: One drug spanning two specialties, rheumatology and gastroenterology, through the same 5-ASA-releasing chemistry. [3]
- 4. Drug: Leflunomide
- 4. Organism: Not applicable
- 4. Indication: Active rheumatoid arthritis in adults
- 4. Line: first-line alternative to methotrexate
- 4. Note: Requires pregnancy exclusion before starting in anyone of reproductive potential, and effective contraception throughout treatment and any elimination procedure. [4]
- 5. Drug: Methotrexate and hydroxychloroquine together
- 5. Organism: Not applicable
- 5. Indication: Combination conventional-DMARD therapy in rheumatoid arthritis and, per rheumatology classification sources, in lupus nephritis regimens alongside other agents
- 5. Line: combination
- 5. Note: Conventional DMARDs are also the base onto which a biologic or a JAK inhibitor is added, rather than a rung that is abandoned once escalation happens. [5]

Pharmacokinetics

- 1. Drug: Methotrexate
- 1. Route: Oral or subcutaneous
- 1. Absorption: Variable oral bioavailability; subcutaneous route used for higher or more reliable exposure
- 1. Csf Penetration: See prescribing reference
- 1. Metabolism: Minimal hepatic metabolism to weakly active metabolites
- 1. Elimination: Primarily renal, unchanged
- 1. Dose Adjust: Renal impairment; monitored by CBC, hepatic and renal function on a fixed schedule [1]
- 2. Drug: Leflunomide
- 2. Route: Oral
- 2. Absorption: Well absorbed; converted to an active metabolite with a very long effective half-life
- 2. Csf Penetration: See prescribing reference
- 2. Metabolism: Rapidly converted to its active metabolite, which undergoes enterohepatic recirculation
- 2. Elimination: Biliary/faecal and renal, slowly, unless accelerated by cholestyramine or activated charcoal
- 2. Dose Adjust: Avoid in pre-existing liver disease or ALT above twice the upper limit of normal [4]
- 3. Drug: Hydroxychloroquine
- 3. Route: Oral
- 3. Absorption: Well absorbed
- 3. Csf Penetration: See prescribing reference
- 3. Metabolism: Hepatic, partial
- 3. Elimination: Renal, with a very long tissue half-life that underlies its cumulative retinal risk
- 3. Dose Adjust: Dose is calculated against actual body weight because daily doses above 5 mg/kg increase retinopathy incidence [2]
- 4. Drug: Sulfasalazine
- 4. Route: Oral
- 4. Absorption: Largely unabsorbed intact; cleaved by gut flora into sulfapyridine (well absorbed) and 5-aminosalicylic acid (largely stays in the gut)

4. Csf Penetration: Not applicable

4. Metabolism: Sulfapyridine is acetylated hepatically; acetylator status affects blood levels

4. Elimination: Renal and faecal

4. Dose Adjust: Adequate fluid intake required to prevent crystalluria; serum sulfapyridine above 50 microgram/mL is associated with more adverse reactions [3]

1. This page gives no dose regimens by design. Doses, escalation schedules and monitoring intervals depend on indication, body weight, renal and hepatic function and response, and belong in a current prescribing reference used by the treating clinician.

2. The one dosing fact treated as a safety point rather than a regimen: methotrexate for rheumatoid arthritis is a weekly medicine, and mistaken daily dosing at the same tablet strength has caused fatal toxicity. This is stated on the label itself, not implied by this page. [1]

3. Leflunomide's active metabolite recirculates enterohepatically and is eliminated so slowly that stopping the tablets alone leaves clinically relevant blood levels for months; an accelerated elimination procedure with cholestyramine or activated charcoal exists specifically to shorten that tail when rapid clearance is needed, confirmed by two plasma levels taken at least fourteen days apart. [4]

Adverse effects

1. Effect: Elevated liver enzymes

1. Detail: Reported with methotrexate (about 15% in rheumatoid arthritis trials), leflunomide (roughly 5 to 10%), and less consistently with sulfasalazine and hydroxychloroquine. [1][4]

2. Effect: Gastrointestinal upset

2. Detail: Nausea and vomiting occur with methotrexate (about 10%); diarrhoea is prominent with leflunomide (17 to 27%); anorexia, nausea and gastric distress affect roughly a third of sulfasalazine-treated patients; nausea, vomiting, diarrhoea and abdominal pain are the most common hydroxychloroquine reactions. [1][4][3][2]

3. Effect: Alopecia

3. Detail: Reported with leflunomide (9 to 17%) and at lower frequency with methotrexate. [4][1]

1. Effect: Bone marrow suppression

1. Detail: Methotrexate can cause unexpectedly severe, sometimes fatal, bone marrow suppression and aplastic anaemia; leflunomide requires platelet and white cell monitoring for the same reason; sulfasalazine has caused deaths from agranulocytosis, aplastic anaemia and other blood dyscrasias, with sore throat, fever, pallor, purpura or jaundice as the labelled symptoms to watch for.

1. Action: Baseline and scheduled complete blood counts are mandatory across the class; any significant decline, or a new sore throat, fever, pallor, purpura or jaundice on sulfasalazine specifically, is a reason to contact the treating clinician promptly rather than to continue dosing unchanged. [1][4][3]

2. Effect: Hepatotoxicity

2. Detail: Methotrexate can cause fibrosis and cirrhosis that may develop without preceding symptoms or abnormal liver tests, chronic toxicity generally following prolonged use above a cumulative dose threshold. Leflunomide's boxed warning includes severe liver injury and fatal liver failure. Sulfasalazine has caused liver necrosis and failure, some fatal.

2. Action: Scheduled liver enzyme monitoring is mandatory across the class; leflunomide is interrupted if ALT rises above three times the upper limit of normal. [1][4][3]

3. Effect: Pulmonary toxicity

3. Detail: Methotrexate-induced lung disease can occur acutely at any time during therapy, even at doses as low as 7.5 mg per week; a new nonproductive cough can be its first sign.

3. Action: New or worsening respiratory symptoms during methotrexate therapy are reported to the treating clinician promptly; a baseline chest X-ray and, where indicated, pulmonary function tests support early recognition. [1]

4. Effect: Interstitial lung disease

4. Detail: Leflunomide carries its own, separately labelled risk of interstitial lung disease, which may be fatal.
4. Action: New or worsening pulmonary symptoms during leflunomide therapy warrant prompt medical evaluation. [4]
5. Effect: Retinal toxicity
5. Detail: Hydroxychloroquine's irreversible retinal damage correlates with cumulative dose and duration, particularly above 5 mg/kg/day, and can continue to progress even after the drug is stopped.
5. Action: Baseline ophthalmic examination within the first year and annual screening after five years of use - earlier and more frequent for higher-risk patients - is how this is caught before it is symptomatic. [2]
6. Effect: Severe cutaneous adverse reactions
6. Detail: Sulfasalazine has caused Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS syndrome, some fatal, with the highest risk in the first month of treatment.
6. Action: A new rash, mucosal ulceration or fever in the first weeks of sulfasalazine therapy is an urgent reason to contact a doctor rather than to wait it out. [3]
7. Effect: Teratogenicity
7. Detail: Methotrexate causes fetal death and congenital anomalies and is contraindicated in pregnancy. Leflunomide's animal data show teratogenicity and embryo-lethality at exposures below the human therapeutic range, and its boxed warning requires pregnancy exclusion before treatment starts.
7. Action: Pregnancy is excluded before either drug is started in anyone of reproductive potential, with effective contraception used throughout treatment; any pregnancy that occurs during treatment is reported to the treating clinician immediately. [1][4]
8. Effect: Opportunistic infection
8. Detail: Methotrexate has been associated with potentially fatal opportunistic infection, including *Pneumocystis jirovecii* pneumonia; sulfasalazine has caused fatal sepsis and pneumonia, particularly alongside myelosuppression.
8. Action: Fever, sore throat or other signs of infection during treatment are reported promptly rather than managed by the patient alone. [1][3]
1. Drug: Methotrexate
1. Effect: Malignant lymphoma has been reported at low, rheumatologic doses and may regress after the drug is withdrawn - an effect specific to this agent within the class. [1]
2. Drug: Hydroxychloroquine
2. Effect: Cardiomyopathy, including fatal cases, and QT prolongation with ventricular arrhythmia risk; hypoglycaemia severe enough to be life-threatening has also been reported. [2]
3. Drug: Sulfasalazine
3. Effect: Reversible oligospermia, and haemolytic anaemia in glucose-6-phosphate dehydrogenase deficiency, alongside an orange-yellow discoloration of urine and skin that is harmless but frequently alarms patients if not anticipated. [3]
4. Drug: Leflunomide
4. Effect: Peripheral neuropathy and hypertension are labelled precautions specific to this drug within the conventional-DMARD group. [4]

Contraindications, precautions and interactions

1. Methotrexate: pregnancy, nursing, alcoholism or chronic liver disease, immunodeficiency syndromes, and pre-existing blood dyscrasias such as marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia. [1]
2. Leflunomide: pregnancy, severe hepatic impairment, and current teriflunomide treatment (teriflunomide is leflunomide's own active metabolite marketed separately). [4]
3. Sulfasalazine: intestinal or urinary obstruction, porphyria, and hypersensitivity to sulfasalazine, its metabolites, sulfonamides or salicylates. [3]
4. Hydroxychloroquine: known hypersensitivity to 4-aminoquinoline compounds. [2]
1. Adequate hydration and, where directed, urine alkalinisation reduce the renal risk of methotrexate precipitating in the

tubules. [1]

2. Diarrhoea and ulcerative stomatitis during methotrexate treatment are reasons to contact the treating clinician promptly, since continuing unmodified risks haemorrhagic enteritis and, rarely, fatal intestinal perforation. [1]

3. Glucose-6-phosphate dehydrogenase deficiency raises the haemolysis risk of both sulfasalazine and hydroxychloroquine, so both are used with closer observation in that setting. [3][2]

4. Leflunomide requires latent tuberculosis screening before treatment, the same infection-screening principle applied to the biologic and targeted synthetic DMARDs that often follow it. [4]

5. Hydroxychloroquine is used cautiously, with cardiac review, in heart failure, prior myocardial infarction, bradycardia, hypokalaemia or concurrent QT-prolonging drugs. [2]

1. With: NSAIDs with methotrexate

1. Effect: High-dose combinations have been associated with unexpectedly severe, sometimes fatal, bone marrow suppression; low-dose rheumatologic combinations are common but still monitored. [1]

2. With: Other hepatotoxic drugs with leflunomide

2. Effect: Caution is advised, given leflunomide's own hepatotoxicity boxed warning. [4]

3. With: QT-prolonging drugs with hydroxychloroquine

3. Effect: Additive risk of ventricular arrhythmia; the combination is avoided where possible. [2]

Comparison tables

Title: Four drugs, four mechanisms, one monitoring habit

Caption: Mechanism and toxicity differ sharply across this class; only the requirement for scheduled laboratory monitoring is genuinely shared. Choice of agent and monitoring schedule belong to the treating clinician.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: mechanism

2. Label: Mechanism

3. Key: signature

3. Label: Signature toxicity

4. Key: monitoring

4. Label: Core monitoring

1. Drug: Methotrexate

1. Mechanism: Dihydrofolate reductase inhibition

1. Signature: Marrow suppression, hepatotoxicity, pneumonitis; fatal if dosed daily instead of weekly

1. Monitoring: CBC, LFTs, renal function, chest X-ray at baseline; CBC at least monthly [1]

2. Drug: Hydroxychloroquine

2. Mechanism: Anti-rheumatic mechanism incompletely understood; well-defined antimalarial action

2. Signature: Cumulative, potentially irreversible retinopathy; rare cardiomyopathy

2. Monitoring: Baseline and (after 5 years) annual retinal exam [2]

3. Drug: Sulfasalazine

3. Mechanism: Anti-inflammatory/immunomodulatory action of its 5-ASA and sulfapyridine fragments

3. Signature: Severe cutaneous reactions (SJS/TEN) early in therapy; blood dyscrasias

3. Monitoring: CBC and LFTs biweekly, then monthly, then quarterly [3]

4. Drug: Leflunomide

4. Mechanism: Dihydroorotate dehydrogenase inhibition (pyrimidine synthesis)

4. Signature: Boxed hepatotoxicity and teratogenicity; a metabolite that needs active elimination

4. Monitoring: ALT and CBC monthly for 6 months, then every 6-8 weeks [4]

High-yield exam pearls

1. Pearl: "Conventional DMARD" is a category of exclusion, not of mechanism.
1. Why: Methotrexate, hydroxychloroquine, sulfasalazine and leflunomide share almost nothing pharmacologically; the label mainly says "invented before biologics." [5]
2. Pearl: Methotrexate for rheumatic disease is a weekly drug - the single most tested safety fact in this class.
2. Why: The label requires both the physician and pharmacist to say this to the patient because mistaken daily dosing at the same tablet strength has been fatal. [1]
3. Pearl: Leflunomide needs an elimination procedure that methotrexate does not.
3. Why: Its active metabolite recirculates enterohepatically for months; cholestyramine or activated charcoal accelerates clearance, verified by two plasma levels 14+ days apart. [4]
4. Pearl: Hydroxychloroquine retinal toxicity can still progress after the drug is stopped.
4. Why: That is exactly why screening exists before symptoms appear rather than after. [2]
5. Pearl: Only sulfasalazine in this class has a true sulfonamide/salicylate allergy contraindication.
5. Why: It is built from both chemistries; the other three conventional DMARDs do not share that specific cross-reactivity risk. [3]
6. Pearl: A conventional DMARD is usually the base a biologic or JAK inhibitor is added to, not a step abandoned at escalation.
6. Why: Combining a conventional DMARD with a biologic is standard; combining two biologics, or a biologic with a JAK inhibitor, is not. [5]

Common exam traps

1. Trap: Assuming this class shares one mechanism because it shares one name.
1. Correction: It does not. Methotrexate blocks dihydrofolate reductase, leflunomide blocks dihydroorotate dehydrogenase, sulfasalazine's action is attributed to anti-inflammatory/immunomodulatory properties not fully characterised, and hydroxychloroquine's anti-rheumatic mechanism remains incompletely understood even though its antimalarial action is well defined. [1][4][3][2]
2. Trap: Treating hydroxychloroquine as the "safe" member of the class with no serious monitoring need.
2. Correction: It carries its own serious, cumulative, potentially irreversible retinal toxicity, plus labelled cardiomyopathy and QT-prolongation risk; it simply is not monitored by blood tests the way the other three are. [2]
3. Trap: Believing methotrexate toxicity only matters at high oncology-range doses.
3. Correction: Pulmonary toxicity has occurred at doses as low as 7.5 mg per week, and bone marrow suppression and hepatotoxicity are labelled risks at ordinary rheumatologic doses too. [1]
4. Trap: Thinking leflunomide's teratogenic risk ends the moment the tablets are stopped.
4. Correction: Its active metabolite persists for months without active elimination, which is precisely why a dedicated cholestyramine or activated-charcoal procedure exists. [4]
5. Trap: Assuming any sulfa-containing drug is interchangeable with sulfasalazine risk-wise.
5. Correction: Sulfasalazine's contraindication is specific to documented sulfonamide or salicylate hypersensitivity, and its severe cutaneous reaction risk is concentrated in the first month of treatment rather than spread evenly across therapy. [3]

Self-test questions

1. Question: A rheumatoid arthritis patient is found taking their methotrexate tablet every day instead of once a week. What is the clinical significance?
1. None - methotrexate has a wide therapeutic index at any interval
2. This is a recognised cause of severe, potentially fatal toxicity, and is exactly the error the label requires prescribers

and pharmacists to warn against

3. It only matters if the patient also takes NSAIDs

4. Daily dosing is actually the correct schedule for rheumatoid arthritis

1. Explanation: The label states plainly that mistaken daily use of the recommended weekly dose has led to fatal toxicity, and requires both physician and pharmacist to emphasise the weekly schedule. [1]

2. Question: Which conventional DMARD's boxed warning includes both teratogenicity and hepatotoxicity, with a distinct elimination procedure for its active metabolite?

1. Hydroxychloroquine

2. Sulfasalazine

3. Leflunomide

4. Methotrexate

2. Explanation: Leflunomide's boxed warning pairs embryo-fetal toxicity with severe hepatotoxicity, and its long-lived active metabolite requires an accelerated elimination procedure with cholestyramine or activated charcoal when needed. [4]

3. Question: Why is hydroxychloroquine retinal screening performed before symptoms appear rather than after?

1. Because the retinal damage is entirely reversible once caught

2. Because irreversible damage can continue to progress even after the drug is stopped

3. Because screening is only a regulatory formality with no clinical basis

4. Because retinal toxicity always presents with pain, making screening unnecessary

3. Explanation: The point of screening is to catch dose-related retinal change before it becomes symptomatic, because progression can continue even after hydroxychloroquine is discontinued. [2]

4. Question: Which contraindication is specific to sulfasalazine and not shared by the rest of the conventional DMARD class?

1. Pregnancy

2. True sulfonamide or salicylate hypersensitivity

3. Chronic liver disease

4. Immunodeficiency syndromes

4. Explanation: Sulfasalazine is a sulfonamide-salicylate hybrid, so documented hypersensitivity to either chemistry is a contraindication specific to this drug within the class. [3]

5. Question: What is the mechanistic basis for calling methotrexate, hydroxychloroquine, sulfasalazine and leflunomide a single class of "conventional synthetic DMARDs"?

1. They all inhibit the same intracellular kinase

2. They all bind the same cell-surface receptor

3. They are grouped by being small synthetic molecules that predate the biologic and JAK-inhibitor era, not by a shared mechanism

4. They are all metabolised by the same hepatic enzyme

5. Explanation: The csDMARD label is a historical and structural grouping - small synthetic molecules developed before biologic and targeted synthetic DMARDs - rather than a statement about a common molecular target. [5]

6. Question: A patient on leflunomide develops a new nonproductive cough with worsening dyspnoea. What does this most urgently raise concern for?

1. A benign, self-limiting side effect requiring no action

2. Interstitial lung disease, a separately labelled and potentially fatal risk of leflunomide

3. Normal drug-related fatigue

4. An expected and harmless finding in all conventional DMARDs

6. Explanation: Leflunomide carries its own boxed-adjacent warning for interstitial lung disease, which may be fatal, and new or worsening respiratory symptoms warrant prompt medical evaluation. [4]

7. Question: Which statement about combining conventional DMARDs with other drug classes in rheumatoid arthritis is

correct?

1. Combining a conventional DMARD with a biologic DMARD is standard and considered safe
2. Combining two biologic DMARDs together is standard practice
3. A biologic DMARD is never combined with any conventional DMARD
4. JAK inhibitors are always combined with a biologic DMARD
7. Explanation: Classification sources describe combination of a biologic with a conventional DMARD such as methotrexate as standard practice, while combining two biologics, or a biologic with a JAK inhibitor, is not recommended. [5]

Frequently asked questions

1. Question: Why is methotrexate given once a week for rheumatoid arthritis instead of daily like most tablets?
1. Answer: Because the rheumatologic dose exploits a different dosing strategy from the daily high-dose regimens used in cancer, and dosing it daily at the same tablet strength has caused fatal toxicity. The label requires both prescriber and pharmacist to emphasise the weekly schedule explicitly to the patient. [1]
2. Question: Is hydroxychloroquine the "safe" conventional DMARD?
2. Answer: It has the lightest burden of marrow and hepatic monitoring in this class, but it is not free of serious risk: cumulative retinal toxicity can be irreversible and can progress even after the drug is stopped, and rare but serious cardiomyopathy and QT prolongation are also labelled. "Lighter blood-test burden" is not the same as "no monitoring needed." [2]
3. Question: Why does leflunomide need a special procedure to "wash out" of the body?
3. Answer: Its active metabolite undergoes enterohepatic recirculation and clears very slowly on its own, staying at clinically relevant levels for months. Where rapid elimination is needed - most importantly if a patient becomes pregnant - cholestyramine or activated charcoal accelerates clearance, confirmed by two plasma levels taken at least 14 days apart. [4]
4. Question: Can these four drugs be used together?
4. Answer: Not typically as a group of four, but combining one conventional DMARD with another, or a conventional DMARD with a biologic, is standard rheumatology practice. What is avoided is combining two biologics together, or a biologic with a JAK inhibitor, because of an unfavourable additional infection risk without a matching efficacy gain. [5]
5. Question: Why does sulfasalazine turn urine and skin an orange-yellow colour?
5. Answer: This is a harmless pigment effect of the drug and its metabolites, explicitly called out in the prescribing information so that patients are not alarmed by it. It is unrelated to the more serious, separately monitored risks of blood dyscrasia and severe skin reaction that the drug also carries. [3]

References

- [1] METHOTREXATE tablet - prescribing information. DailyMed, U.S. National Library of Medicine .
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=02862eb3-5508-4ea9-99fb-262551b6beeb>
- [2] PLAQUENIL (hydroxychloroquine sulfate) tablet - prescribing information. DailyMed, U.S. National Library of Medicine .
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=34496b43-05a2-45fb-a769-52b12e099341>
- [3] AZULFIDINE (sulfasalazine) tablet - prescribing information. DailyMed, U.S. National Library of Medicine .
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ddbe69f3-bd55-45f3-a64f-f60226c744c4>
- [4] ARAVA (leflunomide) tablet, film coated - prescribing information. DailyMed, U.S. National Library of Medicine .
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=320f63f2-fac3-4aee-aff8-85724e00ef52>
- [5] Disease-Modifying Antirheumatic Drugs (DMARDs). StatPearls Publishing / NCBI Bookshelf 2025.
<https://www.ncbi.nlm.nih.gov/books/NBK507863/>

For education only. This guide does not replace professional medical advice. Do not use it to choose or change treatment.