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Review Article

# Chemical Synthetic Disease Modifying Drugs (csDMARD) Used for Rheumatoid Arthritis

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## Abstract

Rheumatoid arthritis is the most common rheumatological disease all over the world. Disease burden, disease-related disability and cost is a significant problem especially for the developing countries. Many advanced and effective treatments including biological drugs are available. However, these biological options are costly and not available in many countries. Hence, traditional disease modifying drugs are still mainstay of treatment for such patients in developing countries. Affordability & availability are major reasons. Physicians managing these cases within limited resources face lot of challenges to control the disease. Junior doctors and trainees often find it hard to understand and prescribe these medications.

This review article focuses on the elaboration of these chemical synthetic DMARDs, their pharmacological details, clinical uses and side effects.

Keywords: csDMARD, Methotrexates, Leflunomide, Hydroxychloroquine, Sulfasalazine.

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## Introduction

## Conventional Synthetic DMARD (csDMARD) for Rheumatoid Arthritis:

### METHOTREXATE (MTX):

**Mechanism:** It works by blocking folate reduction and hence synthesis of purines and pyrimidine affecting cell division: This is the primary mechanism when it works as an anti-cancer drug. Many side effects like bone marrow depression, pregnancy-related issues, hair loss, and GIT mucosal ulceration are due to this effect. MTX also reduces T-cell activation & cytokine production. This is one of the mechanisms of immunosuppression in Rheumatological diseases. MTX reduces adenosine breakdown and increases its effects on adenosine receptors on macrophages, neutrophils, lymphocytes & fibroblasts: The increased adenosine activity reduces TNF-alpha, IL-6, and other inflammatory cytokines. It also increases IL-10, which is an anti-inflammatory cytokine. But increased adenosine activity on fibroblasts increases collagen production and angiogenesis. This could be a mechanism for MTX-related fibrosis in the lungs & liver. So, in simple words, increased adenosine activity blocks inflammatory cells from causing inflammation but can promote a subtle process of non-inflammatory fibrosis. MTX also activates Ito cells and causes fibrosis in the liver. Liver fibrosis can happen independently of any damage to liver cells.

**Dose & route:** Generally, started with 7.5-10 mg/week, then can be increased by 2-5-5mg increments every 2-4 weeks, depending on tolerance and response. The maximum dose is 25-30 mg/week for Rheumatological indications. The cancer dose is very high and is usually 1gm which is repeated. Intolerance or GIT issues are not always dose-related, and some physicians start from a higher dose, such as 25mg/week, right from the start. Subcutaneous is more effective as it has more bioavailability & it can also avoid some of the GIT side effects.

**Why Shouldn't Folate be given same day & why is subcutaneous MTX better than oral?** Reduced Folate transporter (RFC) in the intestinal cells absorbs both folate and MTX; hence if given on the same day, the competition at RFC will reduce MTX absorption. Some people have a genetic polymorphism of RFC, which doesn't absorb MTX well; hence, oral bioavailability is very low (20% or less). Also, subcutaneous MTX can avoid many GIT intolerance-related issues & this leads to increased persistence of MTX treatment with

subcutaneous MTX. For the same reason, response and efficacy also increase with subcutaneous MTX.

**Folate** is given at a dose of 5 mg/week other than when MTX is taken. The dose of folic acid can be increased to minimize the side effects of GIT and the liver. If the side effects are there, the dose of MTX can also be reduced or given as two divided doses per week. Most side effects, such as pancytopenia, GIT symptoms, liver toxicity, alopecia, etc., are due to anti-folate and can be minimized by increasing folate or folinic acid dose.

**First-line DMARD & Anchor Drug:** It, being an anchor drug, is a first-line Disease Modifying Anti Rheumatoid Drug (DMARD) when the diagnosis of RA is established as it's the most effective, more tolerated, safer, and cost-effective among all csDMARD. Also, the long-term experience and safety profile is well shown for MTX. Even when a patient is a candidate for biological DMARDs (bDMARD) or targeted synthetic DMARD (tsDMARD), it's still preferred to continue MTX along with b/ts DMARD, as it gives better outcomes & minimizes the immunogenicity against biological agents.

**MTX** monotherapy is inadequate for a target to treat almost 50-70% of rheumatoid disease activity. Patients with high disease activity, radiological bone erosions, or positive antibodies often need bDMARD or tsDMARD if csDMARD is ineffective.

**Minimum Duration of MTX:** MTX should be given at least six months to see a response. However, a three-month midterm assessment is essential to see some response. If there is a 50% response at three months, it should be continued and assessed at six months.

**Combining MTX with DMARDs:** MTX helps increase the efficacy of most bDMARD by its immunosuppressive role and by reducing antibody formation against biological drugs, giving them the freedom to work without being neutralized by the autoantibodies against the biological drug. MTX is often combined with bDMARD when MTX alone is insufficient to control RA. Most TNF inhibitors and other biological drugs work better when MTX is present. However, Tocilizumab and Tofacitinib have similar efficacy even without MTX and can be used as monotherapy.

**Side Effects of MTX**

- **GIT** mucosal cell damage with ulcerations & mucositis: pain, nausea, vomiting, diarrhea, etc. It often improves with increasing folate, splitting the MTX dose twice a week, changing to a subcutaneous route, or reducing the MTX dose.
- **Hepatotoxic:** Transaminitis, liver fibrosis, and cirrhosis. MTX & Leflunomide are contraindicated in almost all liver diseases. MTX may be conditionally allowed in mild, stable NASH. Increasing folate and MTX dose reduction can help with mild transaminitis. MTX should be stopped for anything more than a 2-fold rise in transaminases.
- **Bone Marrow Suppression:** increasing folate and MTX dose reduction can help with mild but need to stop if more than mild cytopenia.
- **Skin & hair adverse effects:** Increasing folate and MTX dose reduction often help.
- **Teratogenic:** MTX should be stopped six months before becoming pregnant. Folate should continue before and during pregnancy.
- **Pneumonitis, lung disease, etc.:** Folate doesn't help. Should stop the medication. It may need glucocorticoids (GC) for MTX-induced acute pneumonitis.

**Contraindications for MTX**

- Pneumonitis or ILD, airway disease, or lung nodules (see under lungs and rheumatology)
- Bone marrow disease (see under rheumatology and haem)
- Liver disease (see under liver and rheumatology)
- Pregnancy and lactation
- Allergic reaction to MTX

**MTX Toxicity Risks Factors**

- Old age due to decreased metabolism in renal & hepatic, and also reduced immune reserve.
- Renal & liver disease: Excretion and metabolism are affected mainly in renal disease. However, liver disease will affect metabolism and albumin level.
- Low albumin: digoxin is a protein-bound drug.
- Other drugs used, such as NSAIDs & other DMARDs.
- Drug-drug interactions: Bactrim, trimethoprim, or other anti-folate drugs will potentiate MTX toxicity.
- Overdose, wrong dose, daily rather than weekly dose.
- Pre-existing organ disease will predispose to more likelihood of toxicity related to the organ. E.g., pre-existing liver disease will have a higher chance of hepatotoxic effects. Similarly, pre-existing lung disease will increase lung-related toxicity.

**Antidotes for MTX**

1. Folinic acid rescue therapy: folinic acid (an active form of folic acid) is given at a high dose, 5-15mg/day.
2. Another option is using thymidine.

3. Injection glucarpidase is an enzyme that catabolizes MTX into non-toxic metabolites that flush through the kidneys. It is indicated for severe toxicity with a high serum level of MTX. It works rapidly and can reduce MTX levels in minutes to hours. However, it's a costly drug & not always available in many countries.

### Leflunomide (Lef)

**Mechanism:** It blocks the mitochondrial enzyme Di-Hydro Orotic Acid Dehydrogenase (DHODH), a rate-limiting enzyme for pyrimidine synthesis. It affects lymphocytic proliferation as lymphocytes need eight times more pyrimidine than any other cell before starting cell division. Other body cells can escape this effect by increasing the uptake of pyrimidines and using salvage pathways.

**Route & metabolism:** It is absorbed almost entirely with non-enzymatic conversion into its active metabolite Teriflunomide. More than 99% of the drug is bound with plasma proteins, and its half-life varies from 5 to 40 days. Half-life is long, and metabolites can be found in the blood after 1-2 years of stopping the drug. It's excreted half in urine and half in bile.

**Dose:** A loading dose of 100mg may be used for the first few days to saturate protein binding sites & it helps to expedite the onset of its effect, but it can increase the side effects too. The usual dose is 10-20 mg/day. Dose adjustment is rarely needed in renal failure; however, caution should be exercised when eGFR is less than 15.

**Uses other than RA:** It's also used for psoriatic arthritis but's ineffective for cutaneous psoriasis. It can be combined with bDMARD or tsDMARD, especially as an alternative to MTX if later is not tolerated or is contra-indicated.

**Side effects:** Leflunomide can also cause neuropathy and hypertension (besides the organ system affected by MTX). The main adverse effects are GIT upset such as diarrhea and pain, mainly due to its enterohepatic circulation, which irritates the ileum and affects GIT mucosal cells. The second common adverse events are skin rash, itching, and other effects. Less common but more severe side effects include hepatic dysfunction, bone marrow depression, neuropathy, hypertension, or pneumonitis. Some of its side effects (hepatic and pulmonary) are due to aryl hydrocarbon receptor activation. Dose reduction or stopping the drug may be needed.

**Washout of the drug:** for serious adverse effects like hepatotoxicity, bone marrow depression, pre-conception, before major surgery, etc., is required by using activated Charcoal (50gm QID for 11 days) or Cholestyramine (8gm TDS for 11 days). However, the washout can increase the risk of disease flare-ups. Patients with a history of using Leflunomide in the past two years should have teriflunomide levels checked before becoming pregnant. If it's still detectable, it must also wash out until the level is undetectable before becoming pregnant. Empirical washout may be an option in countries where drug level is not available.

### Sulfasalazine (SLZ)

**Mechanism:** It's an immunomodulator, anti-inflammatory, and antibiotic drug. It splits into sulphapyridine & 5-Aminosalicylic acid by the bacterial action in the intestine. It also increases adenosine activity like MTX. It also suppresses cytokines (TNF, RANK-L, IL-8, etc.) production from inflammatory cells & also inhibits B-cell function. It's more effective than HCQ but has poor tolerance due to GIT side effects. The risk of infection is low as it is not an immunosuppressant medication, and it has some anti-bacterial properties.

**Dose and uses:** It's used as an alternative to MTX or an adjunct to MTX. The dose is 0.5-2gm/day.

**Side effects & safety:** Dose-related side effects include GIT upset & CNS side effects, which settle with dose reduction, and the drug can later be restarted. It can also cause hypogammaglobulinemia as it reduces B cell function. It can have a dose-dependent effect on male fertility, which reverses once the drug is stopped.

**Idiosyncratic:** Sulfasalazine can cause sulfasalazine allergy and skin rash. Sulfasalazine-related idiosyncratic side effects are hepatitis, pneumonitis, neutropenia, & hemolytic anemia. Any of these will need immediate drug discontinuation and not use it again.

**It's safe in pregnancy;** the max dose in pregnancy is 2 gm, and folate is also needed. Because it's immunomodulatory (not an immunosuppressant) and has an antibiotic role, infection risk is low and can be continued (like HCQ) despite active infection.

### Hydroxychloroquine (HCQ):

**Mechanism:** It's an immunomodulator, antithrombotic and anti-inflammatory drug. It works by alkalinizing the lysosomal pH in macrophages. Hence antigens can't be degraded and presented to the immune system, which reduces the activation of autoreactive T cells and subsequent inflammatory response.

Other mechanisms of HCQ include the following:

- Effect on cutaneous dendrocytes, which have an important role in lupus
- Increased endothelial nitric oxide
- Inhibition of platelet aggregation and arachidonic acid pathway
- Inhibition of antiphospholipid-beta2 glycoprotein on macrophages

- Inhibition of phospholipase enzyme
- Anti-RANK-ligand effect

**Dose & uses:** Dose is calculated based on ideal body weight. However, if the perfect body weight is more than the actual body weight, the exact weight is used to calculate the dose. The dose of HCQ should be a maximum of 5 mg/kg ideal body weight. The dose is often 100-400 mg/day. The dose should be 15% of the standard dose for dialysis patients. Renal disease (GFR<30) or liver disease will need dose reduction as its metabolism & excretion will be affected. Time: It takes 3-6 months for its effect. Smoking reduces its effect; hence smoking cessation should be advised.

It's used as an alternative to MTX for mild RA or can be added as an adjunct to MTX if later is not adequate. It's also used as a must part of SLE treatment (also for Sjogren and anti-phospholipid syndrome) unless it's contraindicated. It has multiple beneficial effects on SLE Antiphospholipid syndrome, lupus-related osteoporosis, lupus nephropathy, lupus activity & relapses, and metabolic benefits of lowering cholesterol and glucose. HCQ is also used for other immune diseases. Examples are cutaneous lupus, antiphospholipid syndrome, primary Sjogren's syndrome, sarcoidosis, and skin manifestations of dermatomyositis.

### Side effects & safety of HCQ

- HCQ deposits in various tissues, including skin, liver, and retina. In addition, it also binds with melanin in the skin and retina. Major risk factors for HCQ toxicity include old age, high doses of more than 5mg/kg/day, and renal or hepatic dysfunction causing reduced clearance. In addition, pre-existing eye disease is a risk factor for retinal complications & similarly, pre-existing myocardial disease is a risk for heart issues. Drug levels can be monitored for compliance, but insufficient data for this recommendation. Quinacrine is another antimalarial used if HCQ causes retinal toxicity or cutaneous side effects.
- HCQ is safe in pregnancy & lactation. The patients are encouraged to continue HCQ in pregnancy due to its effect on reducing relapse of SLE. It also reduces APLS-related issues and can be added to obstetric APLS cases when low-dose aspirin & prophylactic heparin/LMWH are not adequate during pregnancy.
- No infection risk: HCQ is not considered an immunosuppressant drug. Instead, it's an immunomodulator drug, and infection risk is not high while using HCQ.
- Eye-related issues: Retinal Toxicity: Main side effect is dose and duration-dependent retinal deposition, especially in the macula. It can cause dose & duration-dependent cataract and retinal deposition-related side effects, requiring regular eye checkups. The drug should be stopped if there is any sign of retinopathy. Degeneration of the pigment layer of the retina is due to the binding of the HCQ with the pigments. The classic pattern can be a bull's eye appearance. Significant issues are retinal toxicity with damage to the pigment layer of the

**Table 1:** *Summary of csDMARDs*

| Chemical Synthetic Disease Modifying Anti Rheumatoid Drugs (csDMARD): | | | | |
|---|---|---|---|---|
| **Drug** | **Mechanism** | **Dose** | **Use** | **Main Side Effects** |
| **Methotrexate** | Anti-folate, Adenosine signaling Controls Cytokine & immune cell functions control | 10-25mg/week, PO | First-line DMARD in RA | Hepatotoxic Pneumonitis, ILD Pancytopenia GIT mucosal Damage Hair loss Teratogenic |
| **Hydroxy-chloroquine** | immunomodulator, antithrombotic and anti-inflammatory | 100-400mg daily, PO. | Monotherapy for Mild RA Combination with other csDMARDs. | Retinal toxicity Skin discoloration QT prolongation |
| **Leflunomide** | Blocks mitochondrial enzyme Di-Hydro Orotic Acid Dehydrogenase (DHODH) & hence pyrimidines synthesis | 10-20 mg daily, PO | Alternative to MTX or combined with other DMARDs, including MTX | Same as Methotrexate PLUS Hypertension, Neuropathy Effect on male fertility. |
| **Sulfasalazine** | antibacterial and immunosuppressive | 0.5-2gm, PO daily | Alternative to MTX or combined with other DMARDs, including MTX. | Allergic skin rash, Idiosyncratic, hepatitis, pneumonitis or neutropenia, or hemolytic anemia. |

Abbreviations: DMARDs (Disease Modifying Anti Rheumatoid Drugs), gm (gram), GIT (Gastro-Intestinal Tract), ILD (Interstitial Lung Disease), mg (milligram), PO (Per Oral), MTX (Methotrexate).

retina and related complications such as cystoid macular degeneration etc. Those with risk factors for retinopathy should be assessed at baseline and then at least annually. Optical Coherent Tomography (OCT) and visual field assessment are needed. Retinal toxicity usually occurs after more than 5-6 years of long-term use. It is almost 20% at 20 years of use and then increases 4-5% yearly. Hence baseline check-up before starting HCQ is needed to exclude any pre-existing retinal issues. Those without any risk factor will need reassessment after 4-5 years and then annually.

- Cardiotoxicity is another issue causing lysosomal dysfunction-related myocardial dysfunction and conduction defects. Drugs that cause prolongation of QTc can also add to prolonged QTc due to HCQ. Baseline ECG is essential to assess QTc. Those at risk will need further assessment, such as Echocardiography and Holter. HCQ has anti-arrhythmic effects as it has some properties of Quinine, a class Ia anti-arrhythmic drug.
- Neurotoxicity is partly contributed by lysosomal dysfunction. Neuronal effects include seizures, psychiatric manifestations, cinchonism-like effects, &/or headaches. However, it is used in cerebral lupus cases as well. Skeletal Muscle weakness: It can also cause myotoxicity presenting with weakness.
- Skin pigmentation due to HCQ should stop the medication. Other skin issues due to HCQ are dryness, itching, skin rash, worsening of cutaneous psoriasis, Steven-Johnson, and Toxic Epidermolysis Necrosis.
- Glucose & cholesterol lowering: HCQ can also cause hypoglycemia. It also causes lower cholesterol by HMG-CoA Reductase inhibition.

### Overlapping Side Effects of csDMARD

**GIT upset:** it's common side for MTX, Leflunomide & Sulfasalazine. Both MTX & Leflunomide can cause mucosal cell damage due to their effect on nucleotide synthesis. Nausea, diarrhea &/or pain are common symptoms. MTX commonly causes nausea, and Leflunomide causes diarrhea due to its enterohepatic circulation. Splitting the MTX dose, subcutaneous MTX, reducing the dose, or increasing folic acid can help. Leflunomide can be taken with food, and dose reduction may be needed. Sulfasalazine also causes dose-dependent GI upset, which is why its poor tolerance. HCQ can also cause GIT upset in some cases, but adjustment helps.

**Liver derangement:** MTX & Leflunomide are notorious for causing liver derangement. This is dose and duration dependent; dose reduction or temporarily holding the drug may help. Liver enzyme monitoring is essential. Fatty liver patients with normal enzymes and liver function tests can conditionally use MTX but need monitoring. Alcohol and other hepatotoxic factors should be controlled. Combining Lef with MTX, NSAIDs, or other hepatotoxic drugs increases the chance of liver insult. Any other pre-existing liver disease would require hepatology team advice. Folate can help if MTX causes liver-related side effects. Leflunomide-related liver dysfunction, significantly ALT rise to 2 times above upper normal, can be managed by reducing the dose. However, if ALT increases more than two times may need to stop the drug, and if it's persistent, a Lef washout will be required. Before starting these medications, screening for HBV, HCV, and pre-existing liver disease is essential. Sulfasalazine can cause hepatitis as an idiosyncratic reaction. This must stop the drug (details under liver and rheumatology section).

**Bone marrow suppression:** MTX & Lef cause dose-dependent, whereas Sulfasalazine causes idiosyncratic marrow suppression and cytopenia to a variable extent. Monitoring with a complete blood count is essential. Folate replacement reduces MTX-related cytopenia; dose reduction/cessation may be needed if it doesn't work. Leflunomide-related mild neutropenia will improve with dose reduction. However, severe neutropenia (ANC < 1) will need to be stopped by the drug and may also need to wash out if it doesn't improve. Sulfasalazine can also cause idiosyncratic hematological side effects, which would warrant permanent cessation of therapy.

**Pneumonitis** is a common side effect of MTX, but Lef can also cause pneumonitis. It's better to avoid MTX if there is a lung disease, but it can be used cautiously if it is mild and stable. Patients with pre-existing lung diseases such as COPD or ILD, or lung nodules are at higher risk of MTX-related lung toxicity. Leflunomide can cause pneumonitis, and the risk is higher in smokers or those with pre-existing ILD or when used with MTX. However, causative relation is not established with Leflunomide; one possibility is that these drugs increase rheumatoid-related lung disease. Sulfasalazine can cause allergic pneumonitis, which would need a cessation of the drug.

**Teratogenic effects:** MTX and Lef are teratogenic and are contraindicated in pregnancy & lactation. MTX should be stopped 3-6 months before conception, and use effective contraceptive methods to avoid pregnancy while on MTX or leflunomide. Folate should continue before and during pregnancy. MTX-related effect on male fertility is not established. Leflunomide should be stopped six months before pregnancy. Lef washes out with Cholestyramine (8gm TDS for at least 11 days but can be needed longer if the blood level of teriflunomide is still detectable). Activated Charcoal can also be used for washout at 50gm QID for 11 days. Sulfasalazine and

HCQ are relatively safe in pregnancy. Folate should be given with Sulfasalazine, and the dose should not exceed 2gm/day.

## DMARDs in Special Clinical Conditions

**Male fertility & csDMARD:** Leflunomide (like sulfasalazine) also affect male fertility. Both partners should use effective contraception while on Leflunomide and at least six months after stopping it. No caution is usually needed; male partners can continue sulfasalazine even when trying ART. However, if ART is unsuccessful, it should be stopped too, and semen analysis should be requested.

**Perioperative csDMARD:** MTX can be continued perioperatively in most cases. Those at risk of pneumonia, such as COPD / ILD patients or those with perioperative falls in renal functions, may need withholding treatment. Those on high doses (25mg/week) will also require temporary dose reduction. Leflunomide has a very long half-life; hence, temporary cessation is not recommended. If a patient is at high risk of infection or a significant surgery warrants stopping Leflunomide, it will need Leflunomide to wash out. Sulfasalazine can be continued perioperatively as it is a short-acting & minimally immunosuppressive drug. However, if there is any potential interaction with other medications, it can be held on the day of surgery. HCQ can be continued as it's not an immunosuppressant.

**Kidneys & DMARD Drugs:** CKD with GFR below 30: avoid methotrexate (MTX) due to decreased excretion and increased toxicity. Patients who develop AKI while on MTX should be given rescue folinic acid therapy to reduce the risk of MTX toxicity and causing cytopenia. Leflunomide is cleared by enterohepatic circulation. Lef is not usually used if GFR is less than 15. HCQ dose is adjusted in renal failure and dialysis patients.

**CNS & Rheum Drugs:** Demyelination disease- avoid TNF inhibitors. H/o progressive multifocal leukoencephalopathy (PML) should avoid rituximab (RTX). Patients candidates for RTX should be screened for PML before starting the drug and monitored for PML.

**Heart Failure & Rheum Drugs:** Heart failure (NYHA III or IV): avoid TNF inhibitors. If the patient is on TNFi and develops heart failure, switching to non-TNF DMARD (b or tsDMARDs) is preferable. Rituximab (RTX) can also worsen heart failure.

**Lymphoma & DMARD:** RTX is the preferred DMARD for lymphoma cases. Avoid methotrexate (MTX), leflunomide & TNF inhibitors if there is a history of lymphoma within five years.

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