

Monitoring DMARDs

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- The mainstay of treatment for inflammatory rheumatic disease involves DMARDs
 - The last 30 years have seen enormous shifts in the use of DMARDs, with earlier initiation in disease course as well as combination strategies
 - Many of the drugs used have potential for harm as well as benefit
 - **Appropriate screening** prior to DMARD initiation, as well as **vigilant monitoring during therapy**, are required to minimize the risk of harm

Key recommendations

- Specific questions were considered in relation to each drug:

What baseline screening is needed prior to drug initiation?

What impact does co-morbidity have for prescribers?

What routine monitoring is needed?

When should therapy be interrupted?

Generic Recommendations before Commencing any DMARD

- The decision to initiate DMARDs should be supervised by an **expert in the management of rheumatic diseases**
- Patients should be provided with **education** about their treatment to promote self-management
- Patients should be advised about the impact of DMARD therapy upon **fertility, pregnancy and breastfeeding**
- **Baseline assessment should include height, weight, BP and laboratory evaluation [CBC), (GFR), (ALT) and/or (AST), albumin**
- Patients should be **assessed for co-morbidities** because these may influence DMARD choice, including evaluation for respiratory disease and screening for occult viral infection
- **Vaccinations** against pneumococcus and influenza are recommended

Prescribing DMARDs in Patients with known Co-morbidities

- Pre-existing lung disease is not a specific contraindication to DMARD therapy(caution is advised when using drugs associated with pneumonitis in patients with poor respiratory reserve)
- In patients with deranged liver biochemistry, hepatotoxic DMARDs should be used with caution, with careful attention to trends in test results
- Patients with chronic viral hepatitis infection should be considered for anti-viral treatment prior to immunosuppressive DMARD initiation
- DMARDs must be used with caution in chronic kidney disease, with appropriate dose reduction and increased frequency of monitoring
- Cardiovascular disease and prior malignancy are not considered contraindications to DMARD therapy

Drug-specific recommendations

Hydroxychloroquine

- **Anti-malarial agents have both immunomodulatory and anti-inflammatory properties**
- In practice, doses of HCQ rarely exceed 400 mg daily
- HCQ and CQ are both cleared by the kidney and the liver
- To reduce the risk of retinal toxicity, dose adjustment is needed for a glomerular flow rate less than 60 mL/min (stage 3 or higher chronic kidney disease)

Toxicity of HCQ(ophthalmologic)

Early eye symptoms : defects in accommodation or conversion or blurred vision

Retinal toxicity is the most feared side effect. Risk factors:

- dosage level too high for weight

- duration of use

- kidney disease

- concurrent tamoxifen use

When advanced, visual loss may be irreversible and may continue despite cessation of the drug because of its long half-life in the retina

Toxicity of HCQ: cont.

- Dermatologic
- Neuromuscular
- Cardiovascular
- Gastrointestinal
- Metabolic

Fertility, Pregnancy, and Lactation with HCQ

- No adverse effects on fertility
- HCQ and CQ FDA Pregnancy Category C(due to long half-life of HCQ, discontinuation of the drug at the time of pregnancy does not avoid fetal exposure)
- Current recommendations are that HCQ may be continued throughout pregnancy, particularly in SLE, where discontinuation could precipitate a flare, which would be dangerous to both mother and baby
- HCQ is also found in low concentration in breast milk, but the American Academy of Pediatrics classifies it as compatible with breastfeeding

Toxicity Monitoring

- baseline screening with CBC, liver transaminases, and creatinine
- baseline examination is advised to rule out underlying ocular pathology
- Vaccination with a yearly influenza vaccine is recommended

Drug Interactions

Caution in diabetic patients on hypoglycemic agents.

HCQ increases digoxin levels.

CQ reduce MTX levels

CQ can interfere with cytochrome P450 enzymes (Metabolism of HCQ is inhibited by cimetidine)

Concomittant use with tamoxifen produces synergism for the risk of retinal toxicity

HCQ should not be prescribed with amiodarone, ciclosporin, droperidol, mefloquine or moxifloxacin.

Cautions:

- Acute porphyrias, elderly, G6PD deficiency,
- may aggravate myasthenia gravis severe GI disorders
- Renal and liver impairment [caution if $\text{eGFR} < 50$. If eGFR 30-50: maximum 75% of dose; eGFR 10-30: 25-50% of dose (equivalent of 150mg daily); $\text{eGFR} < 10$: 25-50% of dose (equivalent of 50-100mg daily)]
- Neurological disorders specially in those with history of epilepsy: may reduce threshold for convulsions
- Avoid antacids within 4h of dose
- May exacerbate psoriasis

Contraindications

- Hypersensitivity
- previous retinal or visual field changes attributable to 4-aminoquinoline agents
- severe liver disease caused by viral hepatitis

SULFASALAZINE

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- Sulfasalazine (SSZ) has anti-microbial and anti-inflammatory properties, but the exact mechanism of action is unknown
 - Sulfapyridine and SSZ are likely the active components in rheumatic disease, and 5-ASA is the active component in ulcerative colitis

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- The bioavailability of standard SSZ is similar to that of enteric-coated SSZ
 - Administration of SSZ with food decreases the blood concentration of both SSZ and sulfapyridine
 - To minimize side effects prescribe 500 mg daily and escalate the dose by 500 mg/day every week to the standard dose of 1500 to 3000 mg

SSZ can inhibit enzymes in the folate-dependent pathway so concomitant administration of folic acid may be beneficial

Toxicity

- **Gastrointestinal and Hepatic:** nausea vomiting/ abd. Pain/diarrhea /elevation of transaminases
- **Hematologic :** leukopenia thrombocytopenia macrocytosis hemolysis
- **Dermatologic:** Rash, usually in the first 3 months of Desensitization to SSZ has been reported. erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome Photosensitivity .Patients in whom a rash develops while on SSZ should be cautioned to avoid other sulfonamide-containing agents, such as thiazide diuretics, celecoxib, and antibiotics
- **Pulmonary:** rare , reversible infiltrates with peripheral eosinophilia, cough, dyspnea, fever
- **Rare :** druginduced lupus, hypogammaglobulinemia, and aseptic meningitis
- **Advise patients that they may experience orange discoloration of their urine, sweat, and tears.**

Fertility, Pregnancy, and Lactation

- No effect on fertility in women but men can have oligospermia, impaired sperm motility, abnormal sperm morphology that returns to normal 2 to 3 months after cessation of the drug.
- SSZ is considered FDA Category B, C for pregnancy
- Sulfasalazine is generally considered to be safe to use in pregnancy but doses should not exceed 2g/day and 5mg Folic acid should be prescribed during conception, pregnancy and breastfeeding.
- SSZ does not seem to cause or increase fetal abnormalities or spontaneous abortions, and may be one of the DMARDs of first choice for treating rheumatic disease in women of childbearing age who are or wish to become pregnant

Toxicity Monitoring

Pre-treatment assessment:

- CBC, GFR, ALT and/or AST and albumin.
- Screening for occult viral infections

Monitoring:

- Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin every **2 weeks** until on stable dose for 6 weeks;
- Once on stable dose, **monthly** FBC, creatinine/calculated GFR, ALT and/ or AST and albumin for 3 months;
- Thereafter, FBC, creatinine/calculated GFR, ALT and/or AST and albumin **at least every 12 weeks for 12 months**, then no routine monitoring needed.
- More frequent monitoring is appropriate in patients at higher risk of toxicity
- Pneumococcal Vaccination at the initiation of therapy, and yearly influenza vaccination

Sulfasalazine should be WITHHELD if any of the following occur

- ☐ WCC $<3.5 \times 10^9/L$
- ☐ Platelets $<100 \times 10^9/L$
- ☐ Mean cell volume >105
- ☐ Unexplained reduction in albumin
- ☐ Neutrophils $<1.6 \times 10^9/L$
- ☐ Unexplained eosinophilia $>0.5 \times 10^9/L$
- ☐ ALT $>$ twice upper limit of reference range
- ☐ Rash or oral ulceration
- ☐ Renal impairment: Creatinine increase $>30\%$ over 12 months and/or unexplained reduction in calculated GFR:
stop drug if acute change. If gradual may need dose reduction.
- ☐ Severe sore throat, abnormal bruising: immediate CBC and withhold until the result of CBC is available

Drug Interactions

- May impair absorption of digoxin and decrease its bioavailability
- SSZ increase the effects of oral hypoglycemic
- Increase anti-coagulant effects of warfarin
- Co-prescription of azathioprine may contribute to bone marrow toxicity
- Broad-spectrum antibiotics may alter gut flora and decrease the bioavailability of sulfapyridine and 5-ASA through reduced cleavage of the azo bond.

Methotrexate

Pharmacology

- Administer as PO or SQ or IM
- once the oral dose exceeds 15 mg/wk, absorption diminishes by 30% (If the oral dose of MTX exceeds 15 mg, consideration should be given to splitting the dose)
- Absorption is not reduced by concomitant food intake,
- Milk has inhibitory effect on absorption
- reduced in the setting of intestinal pathology
- Parenteral route prefer to oral route
- MTX accumulates in third-space fluids, which can serve as a reservoir for redistribution into the circulation long after the last dose is administered

Toxicity

- **Gastrointestinal and Hepatic Side Effects:(risk factors:**Alcohol consumption, α 1–anti-trypsin deficiency, morbid obesity, diabetes, concomitant hepatotoxic drugs, and chronic hepatitis B or C)
- **Hematologic :(risk factors** :decreases in renal function. hypoalbuminemia, dosing errors, and concomitant use of probenecid or trimethoprim/sulfamethoxazole)
- **Pulmonary Side Effects**
- **Mucocutaneous Side Effects**
- **Malignancies. Methotrexate Flu. Nodulosis.**

Contraindications

- Significantly impaired hepatic function / alcoholism; liver disease;
- ☐ Pregnancy/planned pregnancy within 3-6 months of treatment (men & women), breast feeding;
- ☐ Pre-existing blood dyscrasias;
- ☐ Significantly impaired renal function (eGFR <30 /mL/min/1.73m²);
- ☐ Previous methotrexate induced lung disease;
- ☐ Known allergic hypersensitivity to methotrexate or other excipients;
- ☐ Serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes, ulcers of the oral cavity and known active gastrointestinal ulcer disease,
- ☐ Live vaccines are contra-indicated during treatment with methotrexate

Pregnancy and Breast feeding

- Methotrexate is teratogenic and there is a theoretical risk of sperm mutation in males, therefore methotrexate should not be used during conception or pregnancy
- Patients of either gender should use adequate contraception during treatment and wait for at least 3-6 months after discontinuation of methotrexate before trying to conceive.
- Methotrexate is contra-indicated during breast feeding

Monitoring

- Baseline tests: CBC, full LFTs, CRP (for rheumatology patients only)
- Remind patients at each visit to report any abnormal bruising, dyspnea, cough, fever, and presence of oral ulceration or sore throat
- Caution : If CRP is significantly and persistently raised above what is normal for that patient, the first step is to consider infection, and ask the patient about a flare in symptoms of their disease. If infection is present, this should be treated and blood tests then repeated. If there is no apparent explanation for the elevated CRP, this should be repeated a few weeks later

Interactions

- **PATIENTS SHOULD NEVER RECEIVE TRIMETHOPRIM OR CO-TRIMOXAZOLE WHILST ON METHOTREXATE** due to risk of significant bone marrow suppression

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- Alcohol: patients are generally advised not to consume more than 10 units of alcohol weekly whilst on methotrexate. Due to an increased risk of liver damage, patients with psoriasis are advised to abstain completely, particularly if they have additional comorbidities such as diabetes and metabolic syndrome
 - **pneumococcal polysaccharide vaccine & annual inactivated flu vaccine should be given**
 - Live vaccines, e.g. rubella, BCG, small pox, yellow fever, should not be given to patients taking methotrexate

LEFLUNOMIDE

- Is a pro-drug in body converted to teriflunamide
- Leflunomide is immunomodulatory, with the net effect being a reduction in activated T lymphocytes, inhibition of pyrimidine synthesis, inhibits tyrosine kinases, interfering with cell signal transduction
- Leflunomide has the ability to block the activation of nuclear factor- κ B
- Inhibit neutrophil chemotaxis
- Decreases the ratio of MMP-1 to TIMP-1

Absorption and Elimination

- The GI tract and the liver rapidly and completely convert ingested leflunomide into A77 1726.
- A77 1726 has a half-life of approximately 2 weeks
- The proportions excreted by the kidney and the gut are nearly equal
- detectable A77 1726 may be present in the body months or years later
- Oral administration of cholestyramine, 8 g three times daily for 11 days, can lower the apparent half-life of A77 1726 to 1 to 2 days
- activated charcoal, 50 g every 6 hours, can reduce plasma levels by 50% within 24 hours

Toxicity

- **Gastrointestinal and Hepatic Side Effects:** diarrhea, abdominal pain, dyspepsia, and nausea, liver toxicity
- **Cardiovascular Side Effects:** HTN, high cholesterol
- **Dermatology:** skin rash , alopecia
- **Pulmonary:**ILD
- **Hematologic:** pancytopenia
- **Weight loss**

Fertility, Pregnancy, and Lactation

- Leflunomide is rated Pregnancy Category X
- Leflunomide excretion in milk is unknown; therefore nursing mothers should not receive leflunomide

active metabolite of leflunomide may remain in the body for years

Drug elimination process

- Step 1: Administer cholestyramine 8 g PO TID 11 days; the 11 days do not need to be consecutive unless there is a need to lower the plasma level rapidly
- Step 2: Verify plasma levels <0.02 mg/L by 2 separate tests at least 14 days apart; if plasma levels >0.02 mg/L, consider additional cholestyramine treatment
- Without the drug elimination procedure, it may take up to 2 years to reach plasma M1 metabolite levels <0.02 mg/L due to individual variation in drug clearance

Toxicity Monitoring

- Baseline tests:
 - ○ **CBC**
 - ○ **LFTs**
 - ○ **Creatinine**
 - ○ **ESR or CRP**
 - ○ **Blood pressure** (if >140/90 on 2 occasions 2 weeks apart treat before starting leflunomide)
 - ○ **Weight**
 - ○ **Varicella Zoster IgG** in suspected non-immune patients and notify general practitioner as appropriate
 - ○ **Screen for active or latent tuberculosis/hepatitis B/C**

Toxicity Monitoring

- **FBC, LFT, ESR or CRP** every 2 weeks for 6 months and if stable 2 monthly
- If co-prescribed with another immunosuppressant or potentially hepatotoxic agent check **CBC** and **LFT** monthly as appropriate.
- **Blood pressure and weight** at each monitoring visit
- If patient develops symptoms/signs of systemic infection, this should be treated promptly and withhold leflunomide until the infection has cleared. Consider accelerated drug washout if infection is severe or likely to be prolonged

Varicella zoster

- o *Non-immune patients* should avoid contact with people with chicken pox or shingles
- Varicella infection can be severe in immunosuppressed patients, and early systemic anti-viral and supportive therapy may be required
- Suspend leflunomide until recovered, and consider accelerated drug washout if required

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- **Alcohol:** patients are advised that alcohol consumption should be avoided or kept to a minimum, due to the increased potential for liver toxicity
 - **Vaccines:** Live vaccines should be avoided in patients taking leflunomide

Contraindications

- Hypersensitivity to leflunomide
 - Serious infections
 - Pregnant women or women of childbearing potential who are not using reliable contraception
 - Breastfeeding
 - Severe unexplained hypoproteinaemia.
 - Impairment of bone marrow function as indicated by anemia and cytopenias due to causes other than RA and PsA
- Uncontrolled hypertension
 - Severe immunodeficiency states (e.g. AIDS)
 - Impaired liver function due to any cause.
 - Renal impairment (moderate to severe).

Drug interactions

- Cholestyramine /activated charcoal: decrease level of leflunomide
- Rifampin : increase level of leflunomide
- Hepatotoxic, hematotoxic: increase side effect with concomitant use
- Decrease metabolism of Warfarin, tolbutamide, phenytoin
- Potentiate NSAID effect



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