

## ***Department of Rheumatology***

### ***Updated guidelines for the prescription and monitoring of non-biologic DMARDs***

### ***Shared care pathway with primary care***

#### **Document Summary**

The rheumatology departmental guidelines for the prescription and monitoring of non-biologic DMARDs and is a shared care guideline with primary care.

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Developed by: Dr Adrian Peall, Consultant Rheumatologist, Claire Jones, Rheumatology Pharmacist and Dr Rameez Arif, Rheumatology SPR, at Hereford County Hospital Rheumatology Department

#### **Important Note:**

**The Intranet version of this document is the only version that is maintained.**

Any printed copies should therefore be viewed as 'uncontrolled' and, as such, may not necessarily contain the latest updates and amendments.

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## **1. Scope and purpose of the guideline**

The British Society of Rheumatology (BSR), released updated evidence based recommendations in February 2017, for the prescription and monitoring of disease-modifying anti-rheumatic drugs (DMARDs). These guidelines form the basis of this locally agreed shared care pathway between primary and secondary care. The purpose is to ensure safe prescribing of DMARDs, and safe drug monitoring once treatment has been initiated by a specialist. It also sets out responsibilities expected from specialists, GPs, pharmacists and patients, as part of the shared care. This document also aims to provide information on common issues encountered with DMARDs, such as inter-current infection and provides healthcare professionals with guidance in such situations. The following DMARDs are covered in this guidance: apremilast, azathioprine, ciclosporin, cyclophosphamide, hydroxychloroquine, leflunomide, mepacrine, methotrexate, minocycline, mycophenolate mofetil, sodium aurothiomalate (gold), sulfasalazine and tacrolimus. Please note, the monitoring information for apremilast, intravenous cyclophosphamide and subcutaneous methotrexate is included, however these will continue to be prescribed in secondary care.

It is important to note however, that these guidelines have scope for adjustment should the healthcare professionals feel alternative evidence based research may be used in specific patients. In addition, certain drug regimens and monitoring may be different based on individual patient needs – but this should be in agreement with specialists.

## **2. Introduction**

DMARDs are widely used medications in the treatment of inflammatory arthritis and many autoimmune diseases. As well as being frequently used in rheumatology they are also commonly used in other specialties including dermatology, gastroenterology, renal and respiratory medicine.

In rheumatology, DMARDs provide good outcomes for patients suffering from inflammatory conditions including RA, seronegative spondyloarthropathies, connective tissue disorders and vasculitis. The effectiveness of DMARDs in suppressing inflammation and reducing disease activity has dramatically reduced the number of patients with severe disability, chronic pain and end organ damage. Good and effective disease control with DMARDs is essential, however careful introduction and monitoring of DMARDs is equally important in order to reduce the risk of potentially harmful side effects. There is good evidence to show that careful drug monitoring will reduce the risk of potential toxicity, whilst maintaining good disease control. It is also important to note that thorough patient education regarding their medications and potential side effects is imperative. It is the responsibility of all healthcare professionals in primary and secondary care managing such patients to try to achieve this.

### **3. Statement of intent**

All rheumatology patients who are taking non-biologic DMARDs in primary and secondary care should be managed according to this guideline.

### **4. Abbreviations**

- AZA – azathioprine
- CSA – ciclosporin
- CTD – connective tissue disease
- CYC – cyclophosphamide
- HCQ – hydroxychloroquine
- JIA – juvenile idiopathic arthritis
- LEF – leflunomide
- MCTD – mixed connective tissue disease
- MMF – mycophenolate mofetil
- MTX – methotrexate
- PsA – psoriatic arthritis
- RA – rheumatoid arthritis
- SLE – systemic lupus erythematosus
- SSZ – sulfasalazine
- TCL – tacrolimus

### **5. Key responsibilities in shared care arrangement**

#### **5.1 Specialist Responsibilities:**

- Initiation of all DMARDs should be by a rheumatology specialist, usually in secondary care.
- At the initiation of treatment, the specialist should counsel and educate patients about the risks and benefits of the DMARDs, and provide appropriate literature (patient leaflets).
- Education and information should also be provided to patients regarding the disease/condition being diagnosed and treated.
- Routine baseline tests should be performed by specialists prior to commencing DMARDs including screen for hepatitis B, hepatitis C and HIV.
- It is the duty of the specialist to promptly notify patients and GPs of any change in their medications and management, and of the actions required of each party.

- If the specialist feels a different monitoring regime is needed based on a patient-to-patient basis, this should be made clear in writing to the GP and patient.

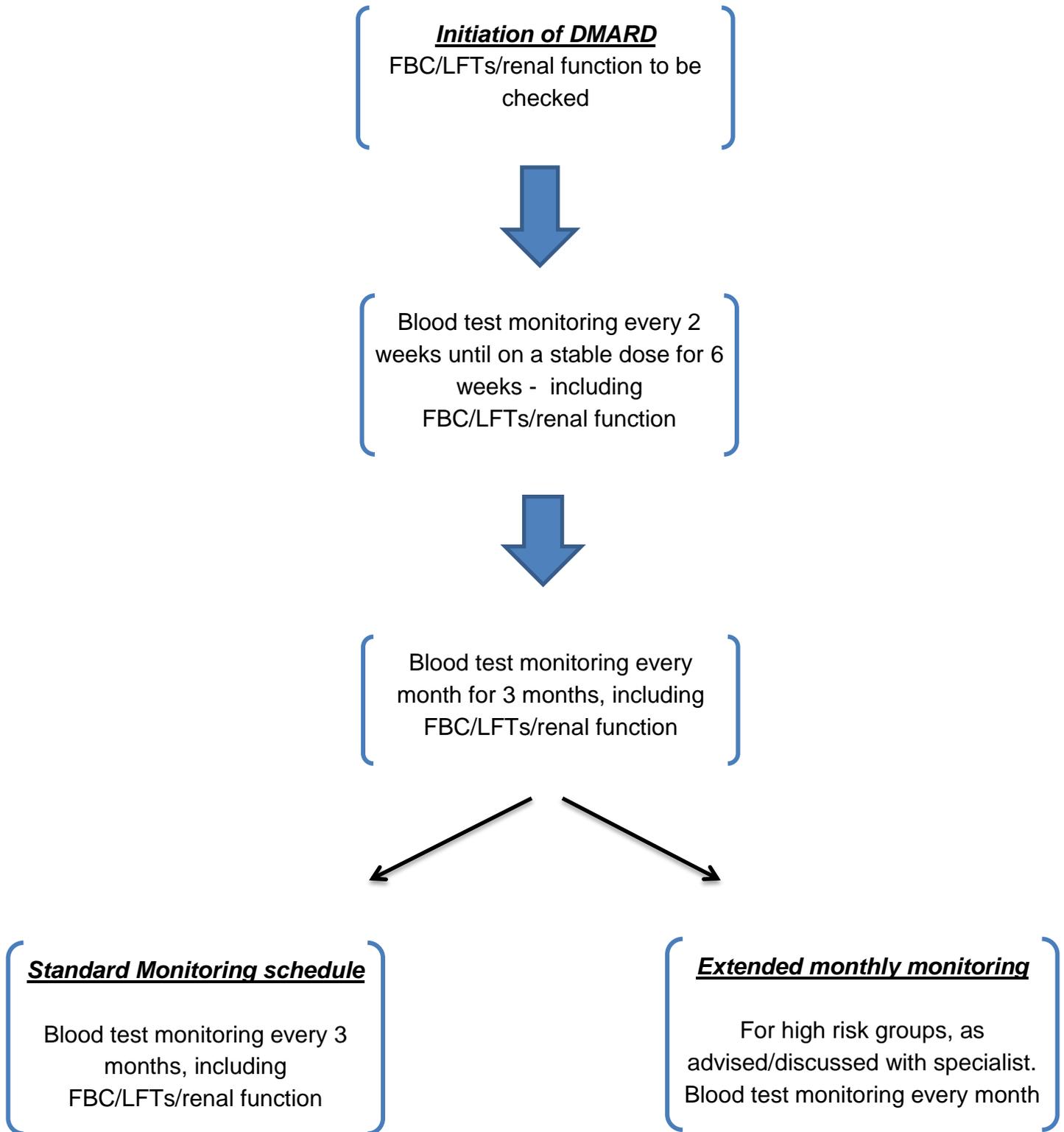
## 5.2 General Practitioners Responsibilities:

- Following initiation of DMARD therapy by specialists, all subsequent repeat prescriptions should be provided by the GP.
- Drug monitoring, as detailed in this guidance, should be undertaken by the GP.
- GPs should contact the rheumatology department urgently if the following develops: WCC <3.5, Neut <1.6, MCV >105, ALT/AST twice upper limit of normal, platelets <140, unexplained albumin <30, unexplained eosinophilia >0.5 or a creatinine increase of >30% over 12 months or any significant decline in renal function.
- GPs (as well as specialists) as the prescribers, have the responsibility for ensuring patients are adhering to monitoring guidance.
- For clinically urgent abnormalities, the rheumatology department should be contacted urgently, and a response within 1 working day is expected.
- GPs should notify the rheumatology department if there are concerns regarding adherence, side-effects, or a deterioration in the patient's condition.

## 5.3 Patient Responsibilities:

- To closely adhere to drug monitoring as advised by GP/specialist.
- To report any potential side effects to GP/specialist.
- To be aware of changes in medication, doses or monitoring schedule.
- Seek advice from GP/specialist if any of the information regarding drug monitoring is not understood.
- Discontinuation of drugs or non-compliance with drug monitoring should be discussed with GP/specialist.

6. Overview of monitoring pathway



## 7. Laboratory monitoring schedules

See overview in Section 6.

DMARD	Laboratory Monitoring	Other Monitoring
<b>Apremilast</b>	No routine laboratory monitoring	MHRA Alert Jan 2017: <i>Risk of suicidal thoughts and behaviour.</i>
<b>Azathioprine (AZA)</b>	Standard monitoring	None
<b>Ciclosporin (CSA)</b>	Extended monthly monitoring longer term <sup>#</sup>	BP and glucose at each monitoring visit
<b>Cyclophosphamide</b>	Full blood count 7, 10 and 14 days after pulsed therapy. For continuous oral therapy, full blood count at fortnightly intervals for the first month of treatment, thereafter every month.	
<b>Hydroxychloroquine (HCQ)</b>	No routine laboratory monitoring	The rheumatology specialist will refer for ophthalmology screening - see individual drug entry for details
<b>Leflunomide (LEF)</b>	Standard monitoring	BP and weight at each monitoring visit
<b>Mepacrine</b>	No routine laboratory monitoring	None
<b>Methotrexate (MTX)</b>	Standard monitoring - review dose with a creatinine increase of >30% over 12 months or any significant decline in renal function.	None
<b>MTX + LEF combined</b>	Extended monthly monitoring longer term <sup>#</sup> and as per methotrexate	As per leflunomide
<b>Minocycline</b>	No routine laboratory monitoring	See individual drug entry regarding headache and visual disturbances
<b>Mycophenolate mofetil (MMF)</b>	Standard monitoring	None
<b>Sodium aurothiomalate (Gold)</b>	Standard monitoring	Urinalysis for blood and protein prior to each dose
<b>Sulfasalazine (SSZ)</b>	Monitoring can be reduced to every 6 months if stable after first year. Then consider stopping completely after 2 years if stable.	None
<b>Tacrolimus (TCL)</b>	Extended monthly monitoring longer term <sup>#</sup>	BP and glucose at each monitoring visit

<sup>#</sup>Patients who have been stable for 12 months can be considered for reduced frequency of monitoring on an individual patient basis

**If a DMARD dose is increased then reverting to the beginning of the monitoring schedule is appropriate.**

## 8. Individual DMARD information and monitoring

### 8.1 Apremilast

#### APREMILAST IS PRESCRIBED IN SECONDARY CARE

**Indications:** PsA

**Dose:** Increasing over 6 days to 30mg BD

**Side effects:** Reduced appetite, decreased weight, cough, depression, suicidal tendencies, diarrhoea, fatigue, GI disorders and discomfort, headaches, increased infection risk, insomnia, nausea and vomiting.

**Additional Information:** *MHRA Alert January 2017* - risk of suicidal thoughts and behaviour. There is an increased risk that some patients may experience psychiatric symptoms with apremilast, including depression and suicidal thoughts. Stop treatment if patients have new psychiatric symptoms or if existing symptoms worsen.

### 8.2 Azathioprine

**Indications:** RA, CTD, vasculitis

**Dose:** 2.5mg/kg per day

**Side effects:** Nausea, pancytopenia, hepatitis, bone marrow depression, pancreatitis.

**Additional Information:** Check baseline TPMT levels prior to commencing.

### 8.3 Ciclosporin

**Indications:** RA, MCTD, vasculitis

**Dose:** 3.5mg per kg. Starting dose 2.5mg per kg.

**Side effects:** Hypertension, progressive renal impairment, marrow suppression, liver enzyme derangement, GI upset and decreased appetite, tremor, hypertrichosis, gingival hyperplasia, fatigue, hair changes, headaches, hyperglycaemia, hyperlipidaemia, hyperuricaemia, skin reactions, oral ulceration

**Additional monitoring:** Check glucose and BP at each monitoring visit.

## 8.4 Cyclophosphamide

### **INTRAVENOUS CYCLOPHOSPHAMIDE IS PRESCRIBED IN SECONDARY CARE**

**Indications:** Vasculitis, SLE and MCTD, RA

**Dose:**

1. "Pulsed" intravenous therapy, e.g. 250 – 1000mg IV (usual dose 10 –15 mg/kg), accompanied by IV steroids. This may be repeated at 2 – 4 weekly intervals depending on toxicity and clinical response. This is always undertaken on an inpatient/day patient basis.
2. "Pulsed" oral therapy. This is usually given as 3 – 5mg/kg on 3 consecutive days every 2 – 4 weeks depending on toxicity and clinical response. This is usually done in outpatients.
3. Continuous daily oral therapy, usually 50 – 150mg daily.

**Side effects:** Marrow toxicity, neutropenia, nausea and vomiting, alopecia, haemorrhagic cystitis, risk of infertility, increased risk of malignancy, hepatic disorders, sperm abnormalities, progressive multifocal leukoencephalopathy.

**Additional monitoring:** Full blood count 7, 10 and 14 days after pulsed therapy. For continuous oral therapy, full blood count at fortnightly intervals for the first month of treatment, thereafter every month.

## 8.5 Hydroxychloroquine

**Indications:** RA, CTD (SLE)

**Dose:** 200-400mg OD

**Side effects:** Rash, pruritus and increased skin pigmentation, nausea, diarrhoea, ocular toxicity.

**Additional Monitoring:** Current advice states that patient is referred to ophthalmology by the rheumatology specialist for baseline screening (including fundus photography and macular OCT) within 6-12 months of starting treatment. If the patient continues on treatment for ≥ 5 years, the rheumatology specialist is to refer for annual screening to include macular OCT, 10-2 visual field and widefield fundus autofluorescence (FAF).

## 8.6 Leflunomide

**Indications:** RA, psoriatic arthritis

**Dose:** 10-20mg OD maintenance dose.

**Side effects:** Temporary alopecia, weight loss, GI upset, rash, stomatitis, rarely Steven Johnson or TEN, leucopenia, rarely pancytopenia, elevation of liver enzymes (persistent ALT elevation 2 – 3 times the upper limit of normal requires cessation of therapy), mild hypertension, headache, peripheral neuropathy.

**Additional Information:** Weight and BP check at every monitoring visit.

May inhibit the metabolism of warfarin.

## 8.7 Mepacrine

**Indications:** SLE, sarcoidosis

**Dose:** Maximum 100mg TDS

**Side effects:** Aplastic anaemia, CNS stimulation, corneal deposits, dermatosis, dizziness, dermatitis, GI disorders, hepatitis, nail, oral, urine and skin discoloration, visual impairment.

## 8.8 Methotrexate

### **SUBCUTANEOUS METHOTREXATE IS PRESCRIBED IN SECONDARY CARE**

**Indications:** RA, PsA, MCTD, vasculitis.

**Dose:** Starting dose 7.5mg-10mg once weekly. Increments of 5mg every 2 weeks, to final dose decided by specialist (usually 15-25mg). Please only prescribe 2.5mg strength tablets. Co-prescribe 5mg folic acid weekly (minimal dose), the day after MTX.

**Side effects:** Nausea, malaise, rash, GI upset, mucositis, oral disorders, headache, depression, liver fibrosis, pneumonitis, pancytopenia, bone marrow depression, skin reactions.

**Additional Information;** Avoid co-prescription with trimethoprim and co-trimoxazole (Septrin). Patients are advised to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine, and respiratory effects (e.g. shortness of breath).

**Additional Monitoring:** Review dose with a creatinine increase of >30% over 12 months or any significant decline in renal function.

## 8.9 Minocycline

**Indications:** RA

**Dose:** 100mg BD

**Side effects:** angioedema, diarrhoea, headache, Henoch-Schönlein purpura, nausea, vomiting, pericarditis, photosensitivity reaction, skin reactions, exacerbation of SLE.

**Additional Information:** Headache and visual disturbances may indicate benign intracranial hypertension (discontinue treatment if raised intracranial pressure develops).

## 8.10 Mycophenolate Mofetil

**Indications:** RA, MCTD, vasculitis, Behcet's

**Dose:** 500mg OD or BD, increasing to max 3g daily. Usual dose 1-2g daily.

**Side effects:** Alopecia, bone marrow disorders, depression, dyspnoea, electrolyte imbalance, hyperglycaemia, hypo/hypertension, skin reactions, GI upset, UTI, haematuria, pancytopenia, malignancy – skin and lymphoma.

### **Pregnancy and contraception:**

- MMF must be avoided in pregnancy due to the teratogenic effects on the unborn child. Women should use 2 forms of effective contraception during treatment and for 6 weeks after stopping treatment.
- Men (including those who have had a vasectomy) should use condoms during treatment and for at least 90 days after stopping treatment. This advice is a precautionary measure due to the genotoxicity of these products.
- Female partners of male patients treated with mycophenolate mofetil or mycophenolic acid should use highly effective contraception during treatment and for 90 days after the last dose.

### 8.11 Sodium Aurothiomalate (Gold)

**Indications:** RA, JIA

**Dose:** An initial test dose of 10mg Myocrisin IM. The patient should be observed for one hour for signs of an acute reaction. If no adverse effects occur, 50mg should be given each week until a total dose of 1000mg is reached. Depending on clinical response, the frequency is reduced to 50mg every two weeks, eventually reaching a maintenance dose of 50mg every 3 – 4 weeks.

**Side effects:** Vasovagal response, stomatitis, rash, pancytopenia, renal toxicity, GI effects, bone marrow disorders, encephalopathy, hepatic disorders, nerve disorders, rarely pneumonitis.

**Additional information:** Rashes with pruritis often occur after 2 to 6 months of treatment and may necessitate discontinuation.

**Additional monitoring:** Urinalysis for blood and protein prior to each dose.

### 8.12 Sulfasalazine

**Indications:** RA, PsA

**Dose:** 500mg OD, for 1 week. Increase by 500mg each week until 1g BD. May be further increased to 1.5g to 2g BD.

**Side Effects:** Indigestion, nausea, rash, oral ulceration, neutropenia, blood dyscrasias, hepatitis, GI effects, dizziness, stains soft contact lenses yellow, orange coloured urine, altered taste.

**Additional Monitoring:** Blood test monitoring can be reduced to every 6 months if stable after first year. Then consider stopping completely after 2 years if stable.

**Additional Information:** A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.

Patients should report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise that occurs during treatment.

### 8.13 Tacrolimus

**Indications:** Autoimmune diseases - CTD

**Dose:** 1-3mg once daily

**Side effects:** Myalgia, tremor, fatigue, headache, paraesthesia, nausea, infections, skin reactions, alopecia, electrolyte imbalance, embolism and thrombosis, GI disorders, hepatic disorders, respiratory disorders.

**Additional monitoring:** BP and glucose at each monitoring visit.

Tacrolimus levels are to be checked in rheumatology clinic as appropriate

## 9. DMARD Use in Pregnancy and Breastfeeding

	Compatible peri-conception	Compatible with first trimester	Compatible with 2 <sup>nd</sup> /3 <sup>rd</sup> trimester	Compatible with breastfeeding	Compatible with paternal exposure
<b>Corticosteroids:</b>					
Prednisolone	Yes	Yes	Yes	Yes	Yes
Methylprednisolone	Yes	Yes	Yes	Yes	Yes
<b>Antimalarials:</b>					
HCQ	Yes	Yes	Yes	Yes	Yes <sup>a</sup>
<b>DMARDs:</b>					
MTX <20 mg/week	Stop 3 months in advance	No	No	No	*Stop 3 months in advance <sup>a</sup>
SSZ (with 5 mg folic acid)	Yes	Yes	Yes	Yes <sup>b</sup>	Yes <sup>c</sup>
LEF	Cholestyra mine washout, no	No	No	No data	Yes <sup>a</sup>

	Compatible peri-conception	Compatible with first trimester	Compatible with 2 <sup>nd</sup> /3 <sup>rd</sup> Trimester	Compatible with breastfeeding	Compatible with parental exposure
AZA <2 mg/kg/day	Yes	Yes	Yes	Yes	yes
CSA	Yes	Yes <sup>d</sup>	Yes <sup>d</sup>	Yes <sup>a</sup>	Yes <sup>a</sup>
Tacrolimus	Yes	Yes <sup>d</sup>	Yes <sup>d</sup>	Yes <sup>a</sup>	Yes <sup>a</sup>
CYC	No <sup>e</sup>	No <sup>e</sup>	No	No	No
**MMF	Stop 6 weeks in advance	No	No	No	No – see drug monograp h

This table summarises the compatibility of DMARDs in pregnancy and breastfeeding. It has been adapted from the BSR guideline on prescribing drugs in pregnancy and breastfeeding. Please see the full guideline via the link below.

<sup>a</sup>Data are limited. <sup>b</sup>In healthy full-term infants only. <sup>c</sup>Conception may be enhanced by stopping SSZ for 3 months prior to conception. <sup>d</sup>Suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels. <sup>e</sup>Only consider in severe, life-threatening or organ-threatening maternal disease.

\*Our department recommends that MTX should 'ideally' be stopped 3 months prior to conception in paternal exposure.

\*\*MMF should not be used in pregnancy in any rheumatic disease. Patients should be counselled regarding potential harm to the baby with MMF, and should seek physician attention immediately if pregnancy does occur. Women should use 2 forms of effective contraception during treatment and for 6 weeks after stopping treatment.

<https://academic.oup.com/rheumatology/article/55/9/1693/1744535/BSR-and-BHPR-guideline-on-prescribing-drugs-in->

## **10. DMARD use in infections, with vaccines and peri-operatively**

### 10.1 Inter-current infections

During a serious infection, the following DMARDs should be stopped until the patient has recovered from the infection: MTX, LEF, SSZ, AZA, apremilast, MMF, CSA and tacrolimus. Severe infections are those that need hospital admission for example, or IV antibiotics. DMARDs may continue if the infection is deemed to be minor or less serious, such as an uncomplicated urinary tract infection requiring a short course of oral antibiotics.

### 10.2 Perioperative management

Please refer to the trust's 'Peri-operative medicines guideline'. The current recommendation is that if patients on DMARDs require surgery, then DMARDs should not routinely be stopped. Studies involving methotrexate and leflunomide use in the perioperative period have not demonstrated increased complication rate or adverse effects. The data is limited regarding HCQ, AZA, SSZ, MMF and TCL. In patients that are deemed high risk for infection however, decisions should be made on an individual basis, and we advise discussion with the rheumatology team in all peri-operative cases for patients taking MMF, MTX, AZA and cyclophosphamide. High-risk surgical procedures (those that have significant post-operative infection risk) and patient factors including age, frailty and co-morbidities should be taken into account when making such decisions.

For steroid replacement peri-operatively, please refer to the trust's 'Steroid replacement during surgical procedures guideline'. The majority of patients may not require higher doses for prolonged courses post-operatively, however this decision should be managed within the clinical ward team.

### 10.3 Vaccinations

It is safe and advisable for patients on DMARDs to have the pneumococcal and influenza vaccine.

Live vaccines are generally not recommended in patients on immunosuppression. This includes the shingles vaccine and vaccinations for foreign travel such as the yellow fever vaccine.

The Green Book gives specific information regarding the use of live vaccines in those taking the following medication or in those who have taken the treatments in the past 3 months:

Live vaccines should not be administered to individuals on immunosuppressive therapy including:

- Those on high-dose corticosteroids (>40mg prednisolone per day) for more than 1 week
- Those on lower dose corticosteroids (>20mg prednisolone per day) for more than 14 days

- Those on non-biological oral immune modulating drugs e.g. methotrexate >25mg per week or azathioprine >3.0mg/kg/day.

Therefore live vaccines may be administered to those taking lower doses of prednisolone and/or of a shorter course length, or those taking low doses of methotrexate or azathioprine. There is no data to support the use of live vaccines in those taking any other DMARDs and a consultant microbiologist should be consulted as necessary.

## **11. Contact details for specialist help**

Support from rheumatology as urgent or routine can be sought from the following contact telephone numbers. It is advisable that the clinician that the patient is known to be contacted first. If not available, other members of the team can help. Should the patient need urgent same day assessment then the on-call medical team should be contacted, as well as rheumatology, in order to carry out this assessment.

Rheumatology Nurse Specialists 01432 364020

Dr A Peall, Secretary 01432 355444 ext 4019

Dr V Jolliffe, Secretary 01432 355444 ext 4019

Dr S Green, Secretary 01432 355444 ext 5400

Dr M Munir, Secretary 01432 355444 ext 5400

Dr D Rees, Secretary 01432 355444 ext 5400

Rheumatology SPR bleep 020

Claire Jones/Caroline Thomas (Rheumatology Pharmacists) 01432 355444 ext 5112

Medical Registrar Bleep 701 (for acute admissions)

Rheumatology department fax 01432 364449

Email address for advice [Hereford.rheum@nhs.net](mailto:Hereford.rheum@nhs.net)

## 12. References

BNF Online: <https://bnf.nice.org.uk/>

BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs:

<https://academic.oup.com/rheumatology/article/56/6/865/3053478#supplementary-data>

BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids:

<https://academic.oup.com/rheumatology/article/55/9/1693/1744535/BSR-and-BHPR-guideline-on-prescribing-drugs-in>.

The Green Book: Immunisation against infectious disease:

<https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book>

Wye Valley NHS Trust: Peri-operative Medicines Guideline: [https://wvt-](https://wvt-intranet.wvt.nhs.uk/media/48385/peri-operative-medicines-guideline-wvt-v1-final.pdf)

[intranet.wvt.nhs.uk/media/48385/peri-operative-medicines-guideline-wvt-v1-final.pdf](https://wvt-intranet.wvt.nhs.uk/media/48385/peri-operative-medicines-guideline-wvt-v1-final.pdf)

Wye Valley NHS Trust: Steroid replacement during surgical procedures for patients with

adrenal insufficiency: <https://wvt-intranet.wvt.nhs.uk/media/47806/steroid-replacement.pdf>