Milton Keynes Clinical Commissioning Group

Central and North West London NHS
NHS Foundation Trust

Milton Keynes Community Health Services

Milton Keynes University Hospital
NHS Foundation Trust

Working in partnership

SHARED CARE PRESCRIBING GUIDELINE FOR THE USE OF DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

The following DMARDS are covered in this guideline: Azathioprine (AZA), Ciclosporin (CSA), Hydroxychloroquine (HCQ), Leflunomide (LEF), Mepacrine, Methotrexate (MTX), Minocycline, Mycophenolate (MMF), Sodium aurothiomalate (GOLD), Sulfasalazine (SSZ)

NOTES to the GP

This shared care agreement sets out how the responsibility for managing the prescribing and monitoring of disease modifying anti-rheumatic drugs (DMARDs) can be shared between Rheumatology specialists and general practitioners (GPs).

Sharing of care assumes communication between the Rheumatology specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The patient's best interests are always paramount.

The decision to initiate DMARDs should be made by the Rheumatology specialist in collaboration with the patient. DMARDs will then normally be initiated by Rheumatology specialists (first 8 weeks) but may be by GPs in particular circumstances and by mutual agreement

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Introduction and reason for shared care

Disease Modifying Anti-Rheumatic drugs (DMARDs) are added at increasingly early stages in the treatment of rheumatoid arthritis (RA) or other inflammatory arthritis such as (but not limited to) Psoriatic arthritis (PsA) to suppress inflammation; they may be used as monotherapy or in combination. DMARDs are also used for the treatment of other rheumatology conditions (e.g. connective tissue diseases and vasculitis).

A number of these drugs are recommended for prescribing in unlicensed indications. All recommendations are based on the practice of a responsible body of peers of similar professional standing (e.g. British Society for Rheumatology (BSR); see References for full details.

Although these drugs are generally very safe when monitored appropriately they do have the potential for harm as well as benefit. Appropriate screening prior to drug initiation and vigilant monitoring during therapy are required to minimise the risk from harm.

Areas of responsibility

Rheumatology specialist responsibility

1. Provide patient with information on disease /drug treatment options. Explain that some drugs are used outside license.
2. Make the decision to initiate DMARDs in conjunction with the patient / carer.
3. Discuss the benefits and side effects of treatment with the patient / carer.
4. Provide written drug information leaflets to the patient (where appropriate) or direct the patient to an appropriate website e.g. https://www.versusarthritis.org/
5. Explain the intention to share care for drug monitoring.
6. Provide the patient with a DMARD medication patient booklet to facilitate shared care that sets out which blood tests may be required.
7. Carry out pre-treatment assessment, including necessary blood tests and review the results when they are available.
8. Initiate treatment with the DMARD & prescribe the first 8 weeks' medication.
9. Send GP details of baseline assessments and results, recommended/prescribed dose of DMARD, monitoring requirements and a summary of the information that has been given to the patient. Seek agreement to share care.
10. At routine clinic appointments review monitoring and assess response to treatment.
11. Communicate promptly with the GP when treatment is changed and when any changes in monitoring are required.
12. At each review appointment confirm the individual patients monitoring schedule, and at least annually.
13. Have a mechanism to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.
14. Ensure that clear backup arrangements exist for GPs to obtain advice and support.

General Practitioner responsibilities

1. Respond to request from the Rheumatology specialist to share care
2. Prescribe the DMARD at the dose recommended after the first 6-8 weeks of treatment or earlier by mutual agreement.
3. Adjust dose of DMARD as advised by the Rheumatology specialist.
4. Carry out monitoring according to the guideline recommendations.
5. Report results outside the set parameters (section 5.3) to the Rheumatology specialist for advice / further management as appropriate.
6. Ensure the patient is aware of any treatment change and the DMARD medication patient booklet is up to date if available.
7. Seek advice from the Rheumatology specialist on any aspect of patient care that is of concern and may affect treatment.
8. Refer patient to the Rheumatology specialist if his or her condition deteriorates.
9. Stop treatment on the advice of the Rheumatology specialist or immediately if an urgent need to stop treatment arises.
10. Report adverse events to the specialist team.

Pharmacist responsibilities

1. Ensure appropriate dose prescribed with clear directions not 'as directed'.
2. Ensure oral methotrexate is only dispensed in the 2.5mg tablet strength (unless specifically requested by GP/specialist on patient's behalf in exceptional circumstances e.g. patient refuses 2.5mg tablets).
3. Provide advice on adverse effects and any drug interactions with prescription and/or OTC medicines.
4. Issue patient information leaflets where appropriate.
5. Monitor frequency of prescription requests and contact GP if quantities in excess of the prescribed dose are ordered

Patient responsibilities

1. Report to specialist or GP if he/ she does not have a clear understanding or has any concerns in relation to treatment
2. Ensure safe storage and handling of medicine
3. Request repeat prescriptions from GP at least one week in advance of medication running out.
4. Book and attend for blood tests at GP practice at the timings set out in the DMARD medication patient booklet as per advice from a Doctor / specialist nurse.
5. Utilise the DMARD medication patient booklet as a request for the necessary blood tests in Primary Care.
6. Ensure the GP and specialist are aware of any over- the -counter medicines they may be taking.
7. Ensure the DMARD medication patient booklet is brought to each appointment with their GP or specialist
8. Report any adverse effects to the GP or specialist.

Non-compliance may lead to a delay in renewal of prescriptions

2. Pre-Treatment Assessment for All DMARDS

1. Height, Weight, Blood pressure & Urinalysis
2. FBC, U&Es / eGFR / Creatinine, LFT's including Albumin
3. Consider screening for HIV and Hepatitis B and C serology (Before first DMARD and consider for at risk populations* with any DMARD change)
4. Respiratory history and examination (see below) (If abnormal consider imaging / lung function testing)
5. Recommend to the patient and their GP that influenza vaccinations are administered ahead of the influenza season and pneumococcal vaccine is given if the patient has not already received it although primary responsibility for vaccination rests with the GP.
6. Consideration of other co-morbidities / pregnancy status that would influence DMARD choice, including lung disease

**People born or brought up in a country with an intermediate or high prevalence (2% or greater) of chronic hepatitis B. This includes: all countries in Africa, Asia, the Caribbean, Central and South America, Eastern and Southern Europe, the Middle East and the Pacific islands: People who have ever injected drugs: Men who have sex with men: People who may have been exposed to sexually acquired infection: Prisoners, including young offenders.*

3. Further Drug-Specific Pre-Treatment Assessment

Drug	Additional Pre-treatment assessment	Notes
Azathioprine	TPMT (Thiopurine methyltransferase)	TPMT assay does not replace routine monitoring Homozygous deficiency -serious and fatal toxicity- can occur within 6 weeks of starting. Heterozygous deficiency - linked to serious adverse events, symptoms may not be evident until 6 months after starting treatment AZA recommended dose: Normal or high TPMT activity: 1-3mg/kg daily Intermediate TPMT activity: 0.5-1.5mg/kg daily N.B. Absent TPMT activity or very low TPMT activity: Contra-indicated. Avoid, can be fatal
Ciclosporin (Neoral)	Non-fasting Lipids	If BP >140/90mmHg treat according to NICE guidelines before commencing
Gold (Myocrisin/Sodium Aurothiomalate)	Administration of test dose	
Hydroxychloroquine	Patients should have baseline formal ophthalmic examination, ideally including objective retinal assessment for example using optical coherence tomography, within 1 year of commencing an antimalarial drug.	
Leflunomide		If BP >140/90mmHg treat according to NICE guidelines before commencing Leflunomide
Methotrexate (Oral & Subcutaneous)	CXR within 6 months where clinically indicated	Co-prescribe folic acid orally at a minimum dose of 5mg once a week 24-48 hours after the Methotrexate
Mycophenolate Mofetil	Pregnancy test in pre-menopausal women	

4. Summary of DMARDs covered in this guideline and information on whether they require routine monitoring or not.

DMARD INITIATION
The following DMARDS are covered in this guideline:

Azathioprine (AZA)
Ciclosporin (CSA)
Hydroxychloroquine (HCQ)
Leflunomide (LEF)
Mepacrine
Methotrexate (MTX)
Minocycline
Mycophenolate (MMF)
Sodium aurothiomalate (GOLD)
Sulfasalazine (SSZ)

DMARDs that **DO NOT** need routine laboratory monitoring:

- HCQ (Annual eye assessment ideally including optical coherence tomography) if continued for >5 years
- Mepacrine
- Minocycline

DMARDs that **DO** need routine laboratory monitoring:
AZA, CSA, LEF, MTX, MMF, GOLD, SSZ

5. Recommended DMARD Blood Monitoring Schedule when Starting or Adding a New DMARD

For all DMARDs that **DO** need routine laboratory monitoring (i.e. AZA, CSA, LEF, MTX, MMF, GOLD, SSZ) measure the following parameters on DMARD initiation

Parameters	Responsible
Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks	Secondary/Primary Care
Then, once on stable dose, monthly FBC, creatinine/calculated GFR, ALT and/ or AST and albumin for 3 months	Primary Care
Then continue on a standard or extended monitoring schedule as shown below	Primary Care

Extended Monitoring Schedule

FBC / LFT'S / CREATININE / eGFR

MONTHLY IN PRIMARY CARE

This is the agreed default monitoring schedule until advised otherwise by specialist or if uncertain

Standard Monitoring Schedule

FBC / LFT'S / CREATININE / eGFR

QUARTERLY IN PRIMARY CARE

- For patient at low risk of toxicity e.g. normal range blood test parameters, no co-morbidities such as renal impairment / fatty liver
- As specified in secondary care review (at least annually) and communicated to GP by clinical letter

6. Suggested DMARD Monitoring Schedules

Drug	Laboratory monitoring	Other monitoring with each blood test
Azathioprine (AZA)	Standard monitoring schedule	None
Ciclosporin (CSA)	Extended monitoring schedule	BP and Glucose
Hydroxychloroquine (HCQ)	No routine laboratory monitoring	Annual eye assessment ideally including optical coherence tomography if continued for >5 years
Leflunomide (LEF)	Standard monitoring schedule	BP and Weight
Mepacrine	No routine laboratory monitoring	None
Methotrexate (MTX)	Standard monitoring schedule	None
MTX and LEF combined	Extended monitoring schedule	None
Minocycline	No routine laboratory monitoring	None
Mycophenolate (MMF)	Standard monitoring schedule	None
Sodium aurothiomalate (GOLD)	Standard monitoring schedule	Urinalysis for blood and protein prior to each dose
Sulfasalazine (SSZ)	Standard monitoring schedule for 12 months then no routine monitoring needed	None

When to consider a Dose reduction

Consider a dose reduction when patients experience the following side effects from the following drugs

Drug	Side effect
Azathioprine	Nausea, diarrhoea, rash, recurrent infection
Ciclosporin	Mouth ulcers, headache, GI upset, recurrent infection • For raised blood pressure • For raised creatinine 30% above baseline
Hydroxychloroquine	Rashes, Headache, GI upset
Leflunomide	Mouth ulcers, headache, GI upset, rash, recurrent infection • For raised blood pressure •
Methotrexate	Mouth ulcers, rash, nausea, diarrhoea
Sulfasalazine enteric coated	Mouth ulcers, headache, GI upset, recurrent infection

7. Monitoring actions for abnormalities

Notes to GPs:
These parameters are suitable for the majority of patients. For some patients individual parameters may be set by the specialist and communicated to Primary Care where results outside these set limits are medically acceptable (for example a persistently raised stable MCV due to drug therapy where no alternative cause has been identified).

The prescriber has responsibility for ensuring patients are adhering to monitoring guidance and respond to abnormalities of the results

If monitored results fall outside normal ranges, use clinical judgement before referral and consider other factors that may be contributing to the abnormality. If uncertainty and concerns remain seek specialist advice as recommended below.

As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g. gradual decreases in WBC or albumin, or climbing liver enzyme).

Abnormality detected	Recommended action to take
White Cell Count (WCC) <3.5 × 10^9/l	With-hold and discuss with rheumatology team
Mean Cell Volume (MCV) >105 f/L	Check B12, Folate, TSH – if abnormal, treat. If normal, discuss with rheumatology team
Neutrophils <1.6 × 10^9/l	With-hold and discuss with rheumatology team
Creatinine increase >30% above baseline over 12 months and/or calculated GFR <60 ml/min/1.73 m^2	With-hold and discuss with rheumatology team
Unexplained eosinophilia >0.5 × 10^9/l	With-hold and discuss with rheumatology team
ALT and/or AST >100 units/L	With-hold and discuss with rheumatology team
Platelet count <140 × 10^9/l	With-hold and discuss with rheumatology team
Unexplained reduction in albumin <30 g/l	With-hold and discuss with rheumatology team
Urine dipstick protein 2+ or greater	Send MSU. If infection confirmed, treat appropriately. If sterile proteinuria seek advice from rheumatology team
BP > 140/90mmHg	Manage hypertension according to NICE guidance; If on ciclosporin with-hold and discuss with rheumatology team
Abnormal Bruising / Sore Throat	With-hold until FBC result available
Unexplained widespread rash / hair loss	With-hold and seek urgent (preferably dermatological) advice
Unexplained oral ulceration	With-hold and discuss with rheumatology team
Unexplained new increasing dyspnoea or cough *	With-hold and discuss with rheumatology team

* AZATHIOPRINE, CICLOSPORIN, GOLD, LEFLUNOMIDE, METHOTREXATE, MINOCYCLINE, SULPHASALAZINE have pneumonitis listed on SPC. Cases reports of MYCOPHENOLATE pneumonitis exist.

8. Sources of specialist advice and support

Rheumatology Secretary M Azeez	01908 996613
Rheumatology Secretary S Banerjee	01908 996613
Rheumatology Secretary S Bowman	01908 996070
Rheumatology Secretary I Papadaki	01908 996070
Rheumatology Secretary W Smith	01908 006819
Rheumatology Department Helpline	01908 996602
Medicines Information Patient Helpline (M-F 9am-5pm)	01908 995733
Useful websites	
Versus Arthritis https://www.versusarthritis.org/	

9. Additional Information

Notable drug interactions (This list is not exhaustive, refer to BNF and SPC)

- **Trimethoprim** is predicted to increase the risk of side-effects when given with **methotrexate**. Manufacturer advises avoid. Both drugs can increase the risk of nephrotoxicity.
- **Co-trimoxazole** is predicted to increase the exposure to **methotrexate**. Manufacturer advises use with caution or avoid. Seek specialist advice if being used.
- **Methotrexate and Penicillins.** Penicillins are predicted to increase the risk of toxicity when given with methotrexate. Manufacturer advises monitor.
- **Methotrexate and Tetracycline.** Both methotrexate and tetracycline can increase the risk of hepatotoxicity.
- **Allopurinol** potentially increases the risk of haematological toxicity when given with **azathioprine**. Manufacturer advises adjust azathioprine dose. Seek specialist advice.

Vaccinations and DMARDS

Vaccinations against pneumococcus (one off) and influenza (annually) are recommended and should be offered in primary care. Ideally these should be commenced before treatment, but can be given at any time.
Shingles vaccine (Zostavax) is not routinely given to all individuals on DMARDS but where indicated may be used in individuals on less than 20mg of Prednisolone or standard doses of DMARD medications. (NB Doses of DMARDs for rheumatic indications are considered 'standard'). Caution needs to be exercised in patients on Methotrexate. It should not be given to patients on biologic therapies. Other live vaccines are NOT recommended.

Inter-current infection and DMARDS

During infection requiring antimicrobial therapy or hospital admission, the following DMARDS should be discontinued temporarily until the patient has recovered from the infection:
Methotrexate, Leflunomide, Sulphasalazine, Azathioprine, Mycophenolate, Ciclosporin.

Perioperative management of DMARDS

Steroid exposure should be minimised prior to surgical procedures to reduce the risk of infection Increases in steroid dose to prevent adrenal insufficiency are not routinely required DMARD therapy should not routinely be stopped in the peri-operative period, although individualised decisions should be made for high-risk procedures. The BSR Guidelines on DMARD therapy provides authoritative advice on prescribing of DMARDs in the peri-operative period, during pregnancy and in other circumstances.

Malignancy and DMARDS

Prior malignancy is not considered a contra-indication to DMARD therapy

References

1. BSR & BHPR guideline for the prescription and monitoring of non-biologic disease-modifying antirheumatic drugs 2017 https://www.rheumatology.org.uk/Knowledge/Excellence/Guidelines
2. BSR & BHPR guideline on prescribing drugs in pregnancy and breastfeeding – Part 1: standard and biological disease modifying anti-rheumatic drugs and corticosteroids https://www.rheumatology.org.uk/Knowledge/Excellence/Guidelines
3. Summary of Product Characteristics http://www.medicines.org.uk/emc/
4. Reducing the harm caused by oral methotrexate. National Patient Safety Agency. 29 July 2004. Available via www.npsa.nhs.uk/health/alerts
5. Improving compliance with oral methotrexate guidelines. Patient Safety alert 13. National Patient Safety Agency. 1 June 2006. Available via www.npsa.nhs.uk/health/alerts
6. NPSA rapid response report on the risks of incorrect dosing of oral anti-cancer medicines (NPSA/2008/RRR001) www.npsa.nhs.uk/health/alerts
7. Personal Communication with Prof Simon Bowman Sept 2018. Shared the Shared Care Agreement used to support the Locally Enhanced Service in Birmingham.

Shared Care Guideline: Prescribing Agreement for the use of Disease Modifying Anti-Rheumatic Drugs (DMARDS)

(Note: Sections A and B MUST be forwarded to GP and returned by GP back to the hospital together)

Section A: To be completed by the hospital consultant initiating the treatment	
GP Practice Details:	**Patient Details:** Name: …… Address: …… DOB: ……/……/…… Hospital number: …… NHS number (10 digits): ……
Consultant name: …… **Dept:** …… **Contact details**:	
Diagnosis:	**Drug name(s) & dose to be prescribed by GP:**
Next hospital appointment: ……/……/……..	

Dear Dr. ……..,

Your patient was seen on ……/……/……and I have started the above medication for the above diagnosis. I am requesting your agreement to sharing the care of this patient from …../…../…….. in accordance with the (attached) Shared Care Prescribing Guideline.

Please take particular note of Section 2 where the areas of responsibilities for the consultant, GP and patient for this shared care arrangement are detailed.

The patient has been given advice outlining potential aims and side effects of this treatment and the following information leaflet……* supplied or the relevant website ……signposted *(* insert any support materials issued such as patient held monitoring book etc where applicable).* The patient has given me consent to treatment possibly under a shared care prescribing agreement (with your agreement) and has agreed to comply with instructions and follow up requirements.

Please monitor according to this guidance – see sections 5 and 6.

Other relevant information: ……..
……..

Consultant Signature: ……Date: …/…/…..

Section B: To be completed by the GP and returned to the hospital consultant as detailed in Section A above

Please sign and return your agreement to shared care within 14 days of receiving this request

I accept sharing care as per shared care prescribing guideline and above instructions

GP name: ……

GP signature: ……Date: ..…/…../…….

If you are not able to sign at this time please contact the Rheumatology Department within 14 days

(Note: Sections A and B MUST be forwarded to GP and returned by GP back to the hospital together)