NHS Worcestershire

Guidelines for the use of Disease Modifying Drugs (DMARDs)

For use in Rheumatology, Dermatology, Neurology, Gastroenterology, Ophthalmology, Respiratory & Renal Medicine

& Shared Care with Primary Care Providers

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1. Introduction

Disease Modifying Anti-Rheumatic drugs (DMARDs) are added at increasingly early stages in the treatment of rheumatoid arthritis (RA) to suppress inflammation; they may be used as monotherapy or more commonly in combination. DMARDs are also used for the treatment of other rheumatology conditions (e.g. connective tissue disease and vasculitis) and in other specialities, including dermatology, respiratory medicine, neurology, ophthalmology and gastroenterology.

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). Prescribers are advised to discuss with the patient if the medicine is used out of license and document this agreement in the patient's medical record.

Many of the drugs 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.

2. Scope of the Guideline

These guidelines outline suggested, evidenced based recommendations for prescribing synthetic, non-biological DMARDs. They incorporate shared care arrangements highlighting the responsibilities of each party (patient, secondary care, primary care). These guidelines are not intended to be a comprehensive review of DMARD therapy. Clinicians should consider nationally published guidelines such as BSR/BHPR (British Health Professional in Rheumatology)Non-biologics guidelines in their practice. The document sets out an agreed approach to implement these standards locally. Please consult the manufacturer's Summary of Product Characteristics (SPC) and the current BNF for full prescribing information on contra-indications, side-effects and interactions. The guidelines do not cover the initiation of biological therapy or the use of drugs in pregnancy (see separate BSR guideline / discuss with specialist). **DMARDs should be initiated by hospital specialists only and should not be initiated in the Primary Care setting.** 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 doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

Where off-license drugs are used outside of usual accepted practice and specialist guidelines, shared care should not be assumed and the patients' GP should be asked in writing if they are prepared to undertake shared care arrangements. Total responsibility for prescribing and monitoring the DMARD remains with the specialist until the GP has responded.

The DMARDs covered by this guideline have been deemed to be appropriate for shared care by the Worcestershire Area Prescribing Committee. It is anticipated that GPs will prescribe DMARDs and participate in shared care in accordance to the written instructions given by the Acute Trust Specialists once the patient has been on treatment for at least 6 weeks. If the GP is not confident to undertake these roles, due to concerns on an individual patient basis, then they should inform the specialist as soon as possible and the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.

3.Responsibilities of Speciality Team, GP Team, Pharmacy Team & Patient

Specialist Responsibilities

1. Provide patient with information on disease /drug treatment options. Explain where 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).
5. Explain the intention to share care for drug monitoring.
6. Provide the patient with a DMARD medication Patient Passport to facilitate shared care and sets out which blood tests required.
7. Carry out pre-treatment assessment, including necessary blood tests and review the results.
8. Initiate treatment with the DMARD & prescribe the first 8 weeks' medication.
9. Arrange tests and review the results for the first 6 weeks monitoring.
10. Send GP details of baseline assessments and results, prescribed dose of DMARD, monitoring requirements and a summary of the information that has been given to the patient.
11. At first routine clinic appointment review monitoring results and assess response to treatment.
12. Communicate promptly with the GP when treatment is changed and when any changes in monitoring are required.
13. At each review appointment confirm the individual patients monitoring schedule, and at least annually.
14. Have a mechanism to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.
15. Ensure that clear backup arrangements exist for GPs to obtain advice and support.

General Practitioner responsibilities

1. Prescribe the DMARD at the dose recommended after the first 6-8 weeks of treatment.
2. Carry out monitoring according to the guideline recommendations
3. Report results outside the set parameters (section 5.3) to the hospital specialist for advice / further management as appropriate.
4. Ensure the patient is aware of any treatment change and the Patient Passport is up to date.
5. Seek advice from the specialist on any aspect of patient care that is of concern and may affect treatment.
6. Refer patient to specialist if his or her condition deteriorates.
7. Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises.
8. 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.
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 Patient Passport as per advice from a Doctor / specialist nurse.
5. Utilise the Patient Passport 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 Patient Passport is brought to each appointment with their GP or specialist
8. Report any adverse effects to the GP or specialist.

4.1 Pre-treatment Assessment (Secondary Care)

PRE-TREATMENT ASSESSMENT FOR ALL DMARDS – TO BE UNDERTAKEN IN SECONDARY CARE

1. Height, Weight, Blood pressure & Urinalysis
2. FBC, U&Es / eGFR / Creatinine, LFT's including Albumin
3. HIV, Hepatitis B and C serology (Before first DMARD for all patients and consider for at risk populations* with any DMARD change)
4. Respiratory history and examination (Rheum patients) (If abnormal consider imaging / lung function testing)
5. Vaccinations against pneumococcus and influenza should be recommended
6. Consideration of 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.*

DRUG	Additional Pre-treatment assessment	Notes
AZATHIOPRINE	TPMT (Thiopurine methyltransferase)	TPMT assay-gives 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 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 TMPT activity : Contra-indication BNF 70, March 2016, page 716
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	Optical coherence tomography (OCT) scan within 1 year of starting	
LEFLUNOMIDE		If BP >140/90mmHg treat according to NICE guidelines before commencing
METHOTREXATE (ORAL & SUBCUTANEOUS)	CXR within 6 months P3NP in dermatology patients	Co-prescribe folic acid orally at a minimum dose of 5mg once a week
MYCOPHENOLATE MOFETIL	Pregnancy test in pre-menopausal women	
TACROLIMUS	ECG	
DAPSONE	G6PD levels Reticulocyte count	

4.2 Monitoring Schedules

4.2.1 DMARD INITIATION

ALL DMARDS THAT REQUIRE MONITORING

FORTNIGHTLY FOR 6 WEEKS IN SECONDARY CARE

FBC / LFT'S / CREATININE / eGFR

MONTHLY FOR 3 MONTHS IN PRIMARY CARE

FBC / LFT'S / CREATININE / eGFR

EXTENDED MONITORING SCHEDULE

FBC / LFT'S / CREATININE / eGFR

MONTHLY IN PRIMARY CARE

(Default until advised otherwise by specialist or if uncertainty.)

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

4.2.2 DOSE INCREASE OF DMARD

FORTNIGHTLY FOR 6 WEEKS IN PRIMARY CARE

FBC / LFT'S / CREATININE / eGFR

RESUME USUAL PATIENT MONITORING SCHEDULE IN PRIMARY CARE

(e.g. monthly / quarterly)

FBC / LFT'S / CREATININE / eGFR

4.2.3 ADDITIONAL MONITORING REQUIREMENTS

To be undertaken with blood tests at frequency set in section 4.2.2 above

DRUG	OTHER MONITORING WITH EACH BLOOD TEST
GOLD (MYOCRISIN/SODIUM AUROTHIOMALATE)	URINALYSIS FOR BLOOD AND PROTEIN WITH EACH INJECTION
LEFLUNOMIDE	BLOOD PRESSURE & WEIGHT
DAPSONE	RETICULOCYTE COUNT
CICLOSPORIN (NEORAL)	BLOOD PRESSURE & BLOOD GLUCOSE
TACROLIMUS	BLOOD PRESSURE & BLOOD GLUCOSE
D-PENICILLAMINE	ASK ABOUT RASH / ORAL ULCERATION
HYDROXYCHLOROQUINE	ANNUAL OCT ASSESSMENT AFTER 5 YEARS USE (TO BE REQUESTED BY SPECIALIST)

4.2.4 SUGGESTED DMARD MONITORING SCHEDULES

To be decided by specialist in Secondary Care and communicated to GP by clinical letter

DRUG	LABORATORY MONITORING
AZATHIOPRINE	STANDARD MONITORING
SULPHASALAZINE	STANDARD MONITORING
GOLD (MYOCRISIN/SODIUM AUROTHIOMALATE)	STANDARD MONITORING
LEFLUNOMIDE	STANDARD MONITORING
METHOTREXATE (ORAL or SUBCUTANEOUS)	STANDARD MONITORING
DAPSONE	STANDARD MONITORING
MERCAPTOPURINE	STANDARD MONITORING
HYDROXYCARBAMIDE	STANDARD MONITORING
LEFLUNOMIDE & METHOTREXATE / HIGHER RISK COMBINATIONS	EXTENDED MONTHLY
MYCOPHENOLATE MOFETIL	EXTENDED MONTHLY
CICLOSPORIN (NEORAL)	EXTENDED MONTHLY
TACROLIMUS	EXTENDED MONTHLY
D-PENICILLAMINE	EXTENDED MONTHLY
HYDROXYCHLOROQUINE	NO ROUTINE MONITORING

4.3 Monitoring - actions for abnormal monitoring parameters

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

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).

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).

Abnormality Detected	Recommended Action to include
WCC <3.5 x 10^9/L	With-hold and discuss with specialist team
Unexplained eosinophilia >0.5 x 10^9/L	With-hold and discuss with specialist team
Neutrophils <1.6 x 10^9/L	With-hold and discuss with specialist team
Platelet count <140 x 10^9/L	With-hold and discuss with specialist team
MCV >105 f/L	Check B12, Folate, TSH – if abnormal treat If normal discuss with specialist team
ALT and/or AST >100 units/L	With-hold and discuss with specialist team
Creatinine >30% above baseline and/or calculated GFR <60ml/min/1.73 m^2	Repeat in 1 week, if still >30% from baseline With-hold and discuss with specialist team
Unexplained fall in serum albumin <30 g/L	With-hold and discuss with specialist team
Urine dipstick protein 2+ or greater	Send MSU. If infection confirmed, treat appropriately. If sterile proteinuria seek advice from specialist team
BP > 140/90mmHg	Manage hypertension according to NICE guidance If on ciclosporin with-hold and discuss with specialist 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 specialist team
Unexplained new increasing dyspnoea or cough *	With-hold and discuss urgently with specialist team
Dapsone	Contact secondary care and consider stopping if Hb decreases by 2g/dL from baseline or reticulocyte count increases >6%
Hydroxycarbamide/urea	Contact secondary care and consider stopping if Hb decreases from baseline >3g/dL. If MCV >105 fl check B12 and folate

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

5. Sources of specialist advice and support

Rheumatology DMARD advice email - wah-tr.dmardadvice-rheum@nhs.net (preferred)

Rheumatology Advice-line Number - 01905 760461

Rheumatology Secretaries WRH - 01905 760454

Rheumatology Secretaries ALEX - 01527 503030

Rheumatology Secretaries KTC - 01562 826353

Dermatology Secretaries WRH - 01905 760157 / 733791

Dermatology Secretaries KTC - 01562 513094 / 828883

Dermatology Secretaries ALEX - 01527 512187

Gastroenterology Help- line Number - 01905 760732 (Answerphone 8.00-3.30pm Mon-Fri)

Gastroenterology Email helen.osinski@nhs.net

Gastroenterology Secretaries WRH - 01905 760623 / 733925 / 733118

Gastroenterology Secretaries ALEX - 01527 512022

Neurology Secretaries WRH - 01905 733729 / 01905 760357

Ophthalmology Secretaries WRH – 01905 760427

Ophthalmology Secretaries KTC – 01562 828852

Renal Secretaries WRH – 01905 733239 / 733494

Renal Secretaries ALEX – 01527 503030 Ext 44618

Respiratory Secretaries WRH – 01905 760240 / 733410 / 733778 / 760237

Respiratory secretaries ALEX – 01527 503030 Ext 44231

6. Additional Information

6.1 Biologics monotherapy monitoring statement

Patients receiving biological therapy require clinical review in secondary care at least every 6 months to allow on-going prescribing of their treatment.

Monitoring blood tests will be undertaken at this appointment in secondary care where indicated.

Therefore, patients on biologics monotherapy DO NOT require drug monitoring in primary care.

6.2 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')

Other live vaccines are NOT recommended.

6.3 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, Apremilast, Mycophenolate, Ciclosporin, Tacrolimus

6.4 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.

6.5 Malignancy and DMARDS

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

7. References

BSR & BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs 2017

https://www.rheumatology.org.uk/Knowledge/Excellence/Guidelines

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

Summary of Product Characteristics http://www.medicines.org.uk/emc/

Reducing the harm caused by oral methotrexate. National Patient Safety Agency. 29 July 2004. Available via www.npsa.nhs.uk/health/alerts

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

NPSA rapid response report on the risks of incorrect dosing of oral anti-cancer medicines (NPSA/2008/RRR001) www.npsa.nhs.uk/health/alerts

NHS Worcestershire Prescribing Policies http://www.southworcsccg.nhs.uk/about-us/area-prescribing-committee/