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Shared Care Guideline for Disease Modifying Anti-Rheumatic Drugs (DMARDs) in Adult Patients with Inflammatory Arthritis (Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Peripheral Spondyloarthritis

DMARDs *(for methotrexate (MTX), sulfasalazine(SSZ) and leflunomide(LEF) only)*

Executive Summary/ Critical Information.

Indication	Route & Dose	Key aims of treatment in the long term	Monitoring undertaken by specialist before requesting shared care	On-going monitoring to be undertaken by GP	Duration of treatment	Stopping criteria	Follow up (weeks/months)
RHEUMATOID ARTHRITIS (RA) **PSORIATIC ARTHRITIS (PSA)** **PERIPHERAL SPONDYLO-ARTHRITIS**	**<u>Methotrexate (MTX)</u>** **2.5mg – 25mg once weekly for RA, PsA and peripheral spondyloarthritis** Unlicensed for PsA and peripheral spondyloarthritis **<u>Sulfasalazine (SSZ)</u>** **500mg – 3g daily in divided doses for RA, PsA and peripheral**	**To induce and maintain remission, and relieve symptoms.**	**Prior to starting DMARD:** **- FBC, U+Es, LFTs** **- Viral serology screen –** **- Hepatitis B sAg/ core Ab** **- Hepatitis C IgG** **- HIV** **- Consider VZV** **- Baseline chest X-ray at discretion of clinician (MTX)** **- Baseline Blood pressure (BP) (LEF)** **The following tests are monitored every 2 weeks for the first 6 weeks (induction phase) and with any increased dose, and then monthly for 3 months:**	**3-monthly monitoring for MTX, SSZ, LEF:** **- FBC** **- Alanine aminotransferase (ALT)** **- Aspartate aminotransferase (AST)** **- Alkaline phosphatase (ALP)** **- Albumin** **- U+Es** **SSZ monitoring can be stopped after 1 year on stable dose.**	**Indefinite**	**Loss of response** **Toxicity/adverse effects** **Interactions with other drugs**	**<u>Hospital Rheumatology Team</u>** **Bloods will be monitored every 2 weeks for the first 6 weeks (induction phase) by the rheumatology specialist team and with any increased dose, and then monthly for 3 months.** **Prescription supplies will be managed by the hospital during the first 3 months induction period (ie for initial 6 weeks and during first 6 weeks of dose escalation or until the patient can be safely moved to Primary Care).** **Patient to be reviewed at least annually by the Rheumatology clinician.**

	spondyloarthritis Unlicensed for PsA and peripheral spondyloarthritis **<u>Leflunomide (LEF)</u>** **Initially 100mg once daily for 3 days and then 10 –20mg once daily for RA and peripheral spondyloarthritis** **Initially 100mg once daily for 3 days and then 20mg once daily for PsA** Unlicensed for peripheral spondyloarthritis		**- FBC** **- Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST)** **- Alkaline phosphatase (ALP)** **- Albumin** **- U+Es** **<u>For MTX, SSZ and LEF:</u>** **After 3 months patients can be switched to 3 monthly monitoring of:** **- FBC** **- ALT/AST/ALP** **- albumin** **- U+Es.** **More frequent monitoring is required in patients at higher risk of toxicity.**				**<u>Primary Care (once patient stable)</u>** **<u>Bloods</u>: Monitor bloods according to recommended schedule** **Issue on-going prescriptions** **<u>Clinical Review</u>: Monitor the patient for loss of response or adverse effects. Monitor BP every 3 months if on leflunomide** **In the event of abnormal bloods including leucopenia, neutropenia, anaemia, renal impairment, elevated ALP, AST or ALT, see section 10.**

Key Safety Notice (for instance: notification if prescribing must be brand specific or BNF cautionary and advisory warnings).

Methotrexate – ONCE WEEKLY dosing. Always prescribe and dispense as **2.5mg tablets**. Additionally, prescribe Folic Acid 5mg ONCE a week (up to SIX times a week to counteract side effects of nausea) not to be taken on the day of methotrexate dose.

For all medications - patients should be warned to report immediately the onset of sore throat, bruising and mouth ulcers, liver toxicity (nausea, vomiting, dark urine and abdominal discomfort) and respiratory effects (cough or shortness of breath)

Other

It is important that patients do not have a break in treatment. In the event of an interruption in supply due to drug shortages, the patient can be restarted on their usual dose without a repeat induction period. A monitoring blood test should be checked after a month before reverting to usual monitoring schedule. Inform the hospital via the rheumatology helpline number.

1. Background

DMARDs are disease-modifying agents to induce and maintain remission in peripheral inflammatory arthritis (rheumatoid arthritis (1), psoriatic arthritis (2,3) and peripheral spondyloarthritis (3)).

Methotrexate is sometimes used in combination with SSZ or leflunomide.

This guideline sets out prescribing and monitoring responsibilities to facilitate shared care of these medications.

2. Contraindications/Cautions

Immunisation with LIVE vaccines	Patients on SSZ and MTX at above doses can generally safely receive immunisation with LIVE vaccines, such as polio, MMR, BCG, Zostavax, or yellow fever (4). Annual influenza vaccination is recommended and pneumococcal vaccination should be considered (1).
Chickenpox/Shingles	Patients who have previously not had chickenpox should avoid contact with those who have ACTIVE chickenpox or shingles and should report any such contact immediately to the hospital specialist to allow a management plan to be made.
Pregnancy/Breastfeeding (5)	Patients planning on becoming pregnant should consult their specialist so that optimal disease control and modification of medical strategy can be considered**. If patient conceives whilst taking these drugs, contact rheumatology department immediately.** Stop MTX 3 months prior to conception. Start folic acid 5mg once daily on stopping MTX. SSZ is safe in pregnancy and breast feeding. Give folic acid 5mg daily in pregnancy. Sulfasalazine may cause transient reversible oligospermia in men. There is less evidence that male patients should stop MTX should they want to father a child and careful discussion with the rheumatology team is recommended. Women planning to have children should either discontinue leflunomide 2 years prior to conception or have a rapid removal of its active metabolite by following the washout procedure (see below). Men should use effective contraception for 3 months after stopping leflunomide. Blood concentrations should be checked prior to planned pregnancy especially if within 2 years of stopping leflunomide or following wash out. Any pregnancy within 2 years of discontinuation of leflunomide should be discussed with the rheumatologist if drug washout has not been performed. MTX and leflunomide are contraindicated during breastfeeding.

Obesity, Diabetes Mellitus or excessive alcohol intake	Increased risk of liver damage
Renal / Hepatic impairment	Dose reduction may be necessary in moderate to severe renal or hepatic impairment.
Perioperative management	DMARDs should not be routinely stopped in the perioperative period and any concerns discussed with the rheumatological team (1).

3. Drug interactions/Side effects

Concomitant use of nephrotoxic, hepatotoxic or myelotoxic drugs should be avoided
For a complete list of cautions/contraindications and drug interactions, please refer to the SPC:
https://www.medicines.org.uk/emc

The active metabolite of leflunomide, A771726, has a long half-life of 1 to 4 weeks. Serious undesirable effects might occur (e.g. hepatotoxicity, haematotoxicity or allergic reactions), even if the treatment with leflunomide has been stopped.

As leflunomide has a long persistence in the body, switching to another DMARD (e.g. methotrexate) without performing the washout procedure (see below) may raise the possibility of additive risks even for a long time after the switching (i.e. drug interactions, organ toxicity).

Similarly, recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects and closer monitoring is recommended in the initial phase after switching.

When such toxicities occur or if for any other reason A771726 needs to be cleared rapidly from the body, the washout procedure must be followed. The procedure may be repeated as clinically necessary. See section 4 for information on washout procedure.

4. Process for Referral Back to Secondary Care

If a GP has taken blood tests for the general medical management of a patient and blood test results fall into any of the categories listed below or the patient reports one of the adverse events listed in section 7, the hospital rheumatology team should be informed using contact details listed in section 10.

Adverse effects	Action
WBC < 3.5 x 10^9/L **Neutrophils < 1.6 x 10^9/L** **Albumin <30g/L (unexplained)** **GFR <60 or creatinine rise >30% over 12 months** **ALT/AST >2x Upper Limit of Normal** **Platelets <140 x 10^9/L**(1)	Consider withholding medication and contact specialist team
MCV > 105 fl	Check vitamin B12, folate and thyroid function tests (TFTs). If low,

	start appropriate supplementation. Check alcohol status. If no cause found, discuss with specialist.
New or increasing dyspnoea or persistent cough (with no other obvious cause – suspected pneumonitis)	**Stop methotrexate**: and discuss with specialist
Rash or oral ulceration	**RASH** - Withhold until symptoms clear. (consider re-challenging at a lower dose) If rash recurs, stop drug and discuss with specialist **MOUTH ULCERS** – Check FBC for leucopenia May respond to increasing folic acid if on MTX or by treating with an OTC mouth ulcer medication. If severe despite extra folic acid stop methotrexate and refer to a specialist for advice.
Hypersensitivity reactions	Fever, malaise, rash, vomiting, muscle/bone pain, dizziness. Stop drug and discuss with specialist.
Abnormal bruising, bleeding or sore throat	Withhold until FBC result available
Nausea, vomiting, diarrhoea	Recommend taking methotrexate tablets after meals to reduce nausea. An anti-emetic or dose reduction may help (or splitting the dose in divided doses). If symptoms persist, stop drug and discuss with specialist.
Suspected infection requiring antibiotics	Check FBC for leucopenia Withhold temporarily until infection clears
Hypertension	If BP >140/90 treat as per NICE guidance. If remains uncontrolled, withhold leflunomide until discussed with rheumatologist.

Leflunomide washout procedure

To aid drug elimination in cases of serious adverse effect or before conception, stop treatment and administer either colestyramine 8g three times day for 11 days or activated charcoal 50g four times a day for 11 days. The duration may be modified depending on clinical or laboratory variables.

Verification by two separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/L and fertilisation is required. See SPC for full information: **https://www.medicines.org.uk/emc**

NB. Leflunomide washout procedure should be discussed with the hospital specialist. All treatments should be provided by the hospital.

5. Monitoring and Responsibilities

a. Hospital specialist:

- Initiate, stabilise and prescribe treatment during the *induction phase* (6 weeks) and until the GP formally agrees to share care (as a minimum, supply the first 6 weeks treatment or until patient is stabilised). This will include monitoring safety, adverse events, and clinical response to therapy as well as drug levels where appropriate.
- Send a letter to the GP requesting shared care for this patient
- Laboratory supervision of the patient on a regular basis for the 6 week induction phase and for 6 weeks following any dose increment.
- Send a letter to the GP after each clinic attendance ensuring current dose and most recent blood results are documented. Where monitoring is via virtual contact, a letter will be sent when to update the GP of any dose change.
- Evaluation of any reported adverse effects by GP or patient.
- Advise GP on review, duration or discontinuation of treatment where necessary.
- Inform GP of patients who do not attend clinic appointments.
- Inform GP, by letter, of clinic visits and action taken for management of patient.

Pre-treatment monitoring	Viral serology screen (HIV, Hepatitis B, Hepatitis C)
	CRP, FBC, Renal profile, ALT and/or AST, ALP
Monitoring during Induction	FBC – every 2 weeks for the first 6 weeks
	Renal profile – every 2 weeks for the first 6 weeks
	ALT/AST/ALP – every 2 weeks for the first 6 weeks

b. General Practitioner/Primary Care:

- Monitor patient's overall health and well-being.
- In times of disease activity/flare ups, inform the hospital specialist.
- After induction, monitor routine bloods (renal profile/liver function tests/FBC/CRP) every 3 months if patient is stable. Refer back to hospital specialist via contact details below if toxicity is suspected – refer to section 8 above
- Provide on-going prescriptions every 3 months as appropriate.
- Report any adverse events to the consultant, where appropriate.
- Report any adverse events via the yellow card scheme, where appropriate.
- Discuss need for annual influenza immunisation and pneumococcal vaccination

c. Patient or parent/carer:

- Ensure they have a clear understanding of their treatment and potential adverse effects.
- Report any adverse effects to their GP and/or hospital rheumatology team
- Report any changes in disease symptoms to GP and/or hospital rheumatology team
- Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy

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6. Contact Information for Advice and Support

	Number
Main switchboard	0207 377 7000
Consultants	Contact details
Consultant Rheumatologists (Mile End Hospital) 1. Dev Pyne 2. Stephen Kelly 3. Frances Humby 4. Maria Bickerstaff 5. Nurhan Sutcliffe 6. Michele Bombardieri 7. Ian Chikanza 8. Ali Jawad 9. Bruce Kidd 10. Costantino Pitzalis 11. Francesco Dell'accio 12. Myles Lewis ***Consultant Rheumatologists (Whipps Cross Hospital)*** 13. Simon Donnelly 14. Angela Pakozdi 15. Sarah Karrar 16. Maliha Shaikh	1. susan.lawrence@nhs.net (Medical Secretary) 2. stephen.kelly5@nhs.net 3. rukhsanapatel@nhs.net (Medical Secretary) 4. susan.lawrence@nhs.net (Medical Secretary) 5. saudah.badat@nhs.net (Medical Secretary) 6. deborah.hession@nhs.net (Secretarial Manager) 7. rukhsanapatel@nhs.net (Medical Secretary) 8. ali.jawad8@nhs.net 9. susan.lawrence@nhs.net (Medical Secretary) 10. deborah.hession@nhs.net (Secretarial Manager) 11. deborah.hession@nhs.net (Secretarial Manager) 12. myles.lewis@nhs.net 13. wxrnh.bartshealth@nhs.net 14. wxrnh.bartshealth@nhs.net 15. wxrnh.bartshealth@nhs.net 16. wxrnh.bartshealth@nhs.net
Clinical Nurse Specialists	0208 223 8407 (Mile End) 0208 535 6664 (Whipps Cross) *Air call via switchboard*
Registrar on –call out of hours	*Air call via switchboard*
Rheumatology Pharmacist	0208 535 6404 (Whipps Cross) Switchboard: 0208 539 5522 Bleep 2975

7. References

1. Ledingham J, Gullick N, Irving K, Gorodkin R, Aris M, Burke J, et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology (United Kingdom). 2017.
2. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis doi:10.1136/annrheumdis-2015-2083372. L Gossec, J S Smolen, S Ramiro et al.
3. Spondyloarthritis in over 16s: diagnosis and management NICE guideline [NG65] Published date: February 2017 Last updated: June 2017
4. Green Book version 13 [Internet]. Public Health England. 2013. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/655225/Greenbook_chapter_6.pdf
5. Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, et al. BSR and BHPR guideline on

prescribing drugs in pregnancy and breastfeeding-Part I: Standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatol (United Kingdom). 2016;

8. Document Management

Document ratification and history	
Produced by:	Bart Health NHS Trust (Dr Dev Pyne - Consultant Rheumatologist/Clinical Lead and Usha Hawker - Specialist Medicine Pharmacist)
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Appendix 1

Shared Care Guideline: Prescribing Agreement	
Section A: To be completed by the hospital consultant initiating the treatment	
GP Practice Details: Name: Tel No: Email (nhs.net):	**Patient Details:** Name: DOB: NHS Number (10 digits):
Consultant Details: Consultant Name: Secretary Contact Details: Tel No: Email (nhs.net):	
Diagnosis:	**Drug Name (to be prescribed by GP):** **Dose:** **Frequency:**
I will review the patient in clinic in weeks / months (*Delete as appropriate)*.	

Dear

Your patient started treatment with the above drug for the above diagnosis on (insert date) and in my view; his/her condition is now stable.

The patient has given consent to treatment under a shared care prescribing agreement and has agreed to comply with instructions and follow up requirements.

I am requesting your agreement to sharing the care of this patient from (insert date) in accordance with the attached Shared Care Prescribing Guideline.

This patient was reviewed on (insert date). These are the results relevant for the drug and/or condition, as outlined in the shared care document:

Test	Baseline	Date

Please continue to monitor the patient as outlined in the shared care guidelines. Refer to the attached guidelines for monitoring criteria.

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 [If returned via e-mail, use NHS.net email account ONLY]

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

☐ Yes, I accept sharing care as per shared care prescribing guideline.

☐ No, I am not willing to undertake shared care for this patient for the following reason:

(Please give reason)

GP Name:	GP Signature:	Date: