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Guidelines

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

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Key words: rheumatic disease, DMARDs, safe prescribing, treatment monitoring, methotrexate, co-morbidity, drug toxicity, shared care.

GUIDELINES

Executive Summary

Scope and Purpose of the Guideline

Need for guideline

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. This current guideline supersedes the previous 2008 BSR/BHPR guideline [1].

Objectives of guideline

The aim is to provide evidence-based recommendations, which do not imply a legal obligation, for clinicians to follow when prescribing synthetic, non-biologic, anti-rheumatic drugs commonly used in management of multi-system rheumatic conditions.

NICE has accredited the process used by the BSR to produce its guidance for the use of non-biologic DMARDs. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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DMARDs covered by this guideline

The following DMARDs are covered in this guideline: apremilast, AZA, CSA, HCQ, LEF, mepacrine, MTX, Minocyline, MMF, sodium aurothiomalate/myocrisin (gold), SSZ and tacrolimus.

Target audience

The target audience is health professionals directly involved in managing patients with rheumatic disease in the UK, including rheumatologists, specialist nurses, pharmacists and general practitioners.

The areas the guideline does not cover

This guideline does not cover the indications for DMARD therapy or the use of biologic therapy and other selective non-biologic DMARDs (e.g. kinase inhibitors). The guideline also does not cover prescribing in relation to pregnancy because this is covered by an existing guideline [2, 3].

Key recommendations from the guideline

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? Recommendations based on systematically reviewed evidence are given below. A description of evidence and full recommendations are given in the full guideline, available at *Rheumatology* online.

Generic Recommendations before Commencing any DMARD

(i) The decision to initiate DMARDs should be made in conjunction with the patient/carer and be supervised by an expert in the management of rheumatic diseases (GRADE 1B, 100%).
(ii) Patients should be provided with education about their treatment to promote self-management (GRADE 1B, 100%).
(iii) When appropriate, patients should be advised about the impact of DMARD therapy upon fertility, pregnancy and breastfeeding (GRADE 1B, 100%).
(iv) Baseline assessment should include height, weight, blood pressure and laboratory evaluation [full blood count (FBC), calculated glomerular filtration rate (GFR), alanine aminotransferase (ALT) and/or asparate aminotransferase (AST), albumin; GRADE 1C, 97%].
(v) Patients should be assessed for co-morbidities because these may influence DMARD choice, including evaluation for respiratory disease and screening for occult viral infection (GRADE 1C, 97%).
(vi) Vaccinations against pneumococcus and influenza are recommended (GRADE 1C, 97%).

Drug-specific Recommendations

(i) MTX: All patients should be co-prescribed folic acid supplementation at a minimal dose of 5 mg once weekly (GRADE 1B, 97%).
(ii) AZA: Patients should have baseline thiopurine methyltransferase (TPMT) status assessed (GRADE 1A, 97%).
(iii) HCQ: 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 (GRADE 2C, 88%).

Prescribing DMARDs in Patients with known Co-morbidities

(i) Pre-existing lung disease is not a specific contraindication to DMARD therapy; however, caution is advised when using drugs associated with pneumonitis in patients with poor respiratory reserve (GRADE 1B, 95%).
(ii) In patients with deranged liver biochemistry, hepatotoxic DMARDs should be used with caution, with careful attention to trends in test results (GRADE 1C, 100%).
(iii) In patients with impaired liver synthetic function (e.g. cirrhosis), DMARD therapy should be used with extreme caution (GRADE 1C, 97%).
(iv) Patients with chronic viral hepatitis infection should be considered for anti-viral treatment prior to immunosuppressive DMARD initiation (GRADE 1B, 99%).
(v) DMARDs must be used with caution in chronic kidney disease, with appropriate dose reduction and increased frequency of monitoring (GRADE 1C, 97%).
(vi) Cardiovascular disease and prior malignancy are not considered contraindications to DMARD therapy (GRADE 1C, 95%).

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

(i) Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks; then 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. More frequent monitoring is appropriate in patients at higher risk of toxicity (GRADE 2B, 97%).
(ii) Dose increases should be monitored by FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks then revert to previous schedule (GRADE 2B, 97%).
(iii) Exceptions/additions to the monitoring schedule for specific DMARDs are included in Table 1 (GRADE 2B and C, 100%).

Table 1 Summary of monitoring requirements

Drug	Laboratory monitoring	Other monitoring
Apremilast	No routine laboratory monitoring	None
AZA	Standard monitoring schedule[a]	None
Ciclosporin	Extend monthly monitoring longer term[b]	BP and glucose at each monitoring visit
Gold	Standard monitoring schedule[a]	Urinalysis for blood and protein prior to each dose
HCQ	No routine laboratory monitoring	Annual eye assessment (ideally including optical coherence tomography) if continued for >5 years
LEF	Standard monitoring schedule[a]	BP and weight at each monitoring visit
Mepacrine	No routine laboratory monitoring	None
MTX	Standard monitoring schedule[a]	None
MTX and LEF combined	Extend monthly monitoring longer term[b]	None
Minocycline	No routine laboratory monitoring	None
Mycophenolate	Standard monitoring schedule[a]	None
SSZ	Standard monitoring schedule for 12 months then no routine monitoring needed	None
Tacrolimus	Extend monthly monitoring longer term[b]	BP and glucose at each monitoring visit

[a]Standard monitoring as per recommendations I and II for DMARD blood monitoring schedule when starting or adding a new DMARD. [b]Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis. BP: blood pressure.

Perioperative DMARD Management

(i) Steroid exposure should be minimized prior to surgical procedures, and increases in steroid dose to prevent adrenal insufficiency are not routinely required (GRADE 2B, 95%).

(ii) DMARD therapy should not routinely be stopped in the perioperative period, although individualized decisions should be made for high-risk procedures (GRADE 2B, 95%).

Intercurrent Infections

(i) During a serious infection, MTX, LEF, SSZ, AZA, apremilast, MMF, CSA and tacrolimus should be temporarily discontinued until the patient has recovered from the infection (GRADE 1A–C, 97%).

Recommendations for Shared Care Agreements

(i) The prescriber has responsibility for ensuring patients are adhering to monitoring guidance (GRADE 1C, 97%).

(ii) When prescribing takes place in primary care, it should be supported by local written shared care agreements, highlighting responsibilities of each party (patient, secondary care, primary care; GRADE 1C, 97%).

(iii) Contact rheumatology team urgently and consider interruption in treatment if any of the following develop: white cell count $<3.5 \times 10^9$/l; mean cell volume >105 fL; neutrophils $<1.6 \times 10^9$/l; creatinine increase >30% over 12 months and/or calculated GFR <60 ml/min; unexplained eosinophilia $>0.5 \times 10^9$/l; ALT and/or AST >100 U/l; platelet count $<140 \times 10^9$/l; unexplained reduction in albumin <30 g/l (GRADE 1C, 99%).

As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g. gradual decreases in white blood cells or albumin, or increasing liver enzymes).

For clinically urgent abnormalities, emergency access to specialist rheumatology advice, with response within one working day, should be available as per National Institute for Health and Care Excellence guidelines.

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Supplementary Data

The full guideline is available as supplementary data at *Rheumatology* Online.

References

1 Chakravarty K, McDonald H, Pullar T *et al*. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheumatology 2008;47:924–5.

2 Flint J, Panchal S, Hurrell A *et al*. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part II: analgesics and other drugs used in rheumatology practice. Rheumatology 2016;55:1698–702.

3 Flint J, Panchal S, Hurrell A *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. Rheumatology 2016;55:1693–7.

Clinical vignette

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Recognizing the clinical triad and dural calcification in adult hypophosphatasia

A 49-year old man who was treated for presumptive ankylosing spondylitis since adolescence presented with a 6 month history of thigh and knee pain. Clinically he had limited lumbar spine movement and patellar tenderness.

Laboratory indices revealed low serum alkaline phosphatase (17 U/l) but normal calcium, phosphate, parathyroid hormone, 25(OH)D and creatinine. HLA-B27 was negative and radiographic sacroiliitis was not present. Lumbosacral spine X-rays showed DISH-like changes (posterior longitudinal ligament calcification, paravertebral bridging, linear calcification and vertebral body hyperostosis). There were proximal right femur and bilateral patellae fractures. A CT scan of his lumbar spine showed spinal dural calcification (Fig. 1). Elevated urinary phosphoethanolamine (PEA; 47 μmol/mmol creatinine) confirmed the diagnosis of adult hypophosphatasia [1, 2]. A review of his family members revealed two siblings with chronic back pain, early loss of deciduous teeth, fragility fractures, low serum alkaline phosphatase, elevated urinary PEA and calcification of the posterior longitudinal ligaments.

A triad of low alkaline phosphatase, pathologic fractures and ectopic calcification should alert the physician to adult hypophosphatasia [1, 2]. In this case, the unusual finding of spinal dural calcification differentiated adult hypophosphatasia from other spine and metabolic bone diseases, thus aiding in diagnosis.

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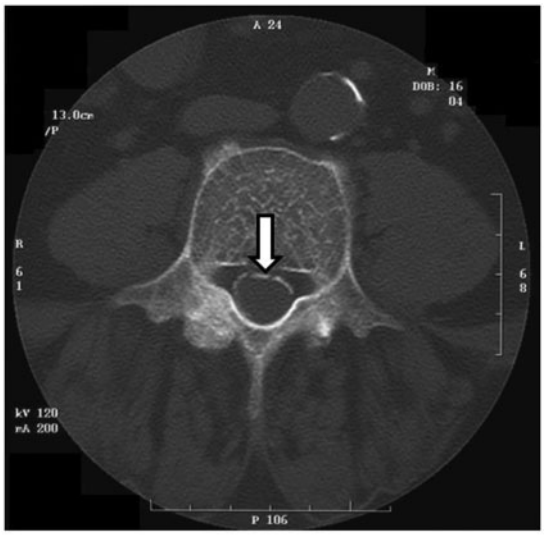
Fig. 1 CT of the lumbar spine showing diffuse calcification of the dura



CT of the lumbar spine showing diffuse calcification of the dura (arrow). The calcification does not lie in the posterior longitudinal ligament, as was originally seen on plain films (data not shown).

References

1 Rathbun JC. Hypophosphatasia: a new developmental anomaly. Am J Dis Child 1948;75:822–31.

2 Whyte MP, Teitelbaum S, Murphy W *et al*. Adult hypophosphatasia. Clinical, laboratory, and genetic investigation of large kindred with review of the literature. Medicine 1979;58:329–47.