 doi:10.1093/rheumatology/kel216b

Guidelines

BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists

K. Chakravarty, H. McDonald[1], T. Pullar[2], A. Taggart[3], R. Chalmers[4], S. Oliver[5,6], J. Mooney[7], M. Somerville[8], A. Bosworth[9], T. Kennedy[10] on behalf of the British Society for Rheumatology, British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group in consultation with the British Association of Dermatologists

KEY WORDS: DMARD, Guideline, Multidisciplinary, Multi professional.

Scope and purpose

Background to disease/the drug therapy

Inflammatory arthritis, and especially rheumatoid arthritis (RA), is common and affects over 1% of the population. Even in the 21st century, the prognosis of RA remains uncertain. It runs a variable and unpredictable course. Several longitudinal studies have demonstrated the progressive course of the disease, leading to joint destruction and deformity and, ultimately, to loss of functional independence and to residual disability. Research has shown that early intervention with disease specific anti-rheumatic drugs, also called second line drugs or disease-modifying anti-rheumatic drugs (DMARDs) is the cornerstone of treatment and, in the early stages may be able to curb or arrest the progressive synovitis and joint destruction and thereby limit disability [1].

This guideline is intended to help clinicians and allied health professionals, both in primary and secondary care, to make decisions about DMARD therapy, with particular reference to their toxicity profile. These drugs are used in a number of conditions, including RA, psoriasis and psoriatic arthritis, as well as the connective tissue diseases and vasculitis. It is essential that DMARDs are used in appropriate doses to achieve an optimal balance between benefit and risk [2].

Need for guideline

The use of DMARDs in rheumatology and dermatology requires the use of guidelines for drug toxicity monitoring, as adverse effects can be significant in some patients. Most specialists recommend regular safety monitoring of these drugs based on clinical experience and the data from published literature, such as Product Specific Characteristics, the British National Formulary (BNF) and publications from various clinical trials in the specialty literature [3–6]. The adverse effects of DMARDs as reported in research trials have limitations, as the patient characteristics are likely to be different from those in daily clinical practice. It is desirable if not necessary, to have some form of guideline which is multidisciplinary with patient participation, using evidence base, peer reviewed, well researched and supported by some study/audit of national practice. In 2000 the British Society for Rheumatology (BSR) produced its second edition of DMARD monitoring guidelines for rheumatologists but this was considered by the committee for evaluation of guidelines of the Royal College of Physicians to be more appropriate as a 'practical tool' than guideline. The need for a review of the guideline is, therefore, not only timely but also of paramount importance as the approach to therapy of many rheumatological and dermatological diseases has changed in the recent years, with greater accumulation of evidence since the last publication. Moreover, the current DMARD guideline has been developed in collaboration with the British Association of Dermatologists (BAD), as there is a common interest to prevent and limit toxicity associated with the use of these drugs in these two specialties.

Objective of the guideline

This guideline provides a list of licensed and unlicensed indications for the use of DMARDs in rheumatology and dermatology. It provides an evidence-based approach with appropriate references to all recommendations in terms of predicting, assessing and counteracting any toxic effects related to the use of the DMARDs in these two specialties.

The main objective of this guideline is to provide clear information that the responsible clinician can use to ensure DMARDs may be safely prescribed and monitored.

It is expected that the guidelines should be viewed with individual drug SPC's (Summary of Product Characteristics)

Harold Wood Hospital, BHR Trust, Romford, [1]Gubbins Lane Surgery, Harold Wood, [2]Ninewells Hospital, Dundee, [3]Musgrave Park Hospital, Belfast, [4]Manchester Royal Infirmary, Manchester, [5]Royal College of Nursing Rheumatology Forum, London, [6]Litchdon Health Centre, Barnstaple, [7]Norfolk & Norwich University Hospital and University of East Anglia, [8]Norfolk & Norwich University Hospital, Norwich, [9]National Rheumatoid Arthritis Society, Maidenhead and [10]Royal Liverpool and Broadgreen University Hospital Trust, Liverpool, UK.

Submitted 19 February 2006; revised version accepted 11 March 2008.

Correspondence to: K. Chakravarty, Harold Wood Hospital, BHR NHS Trust, Romford, Essex, RM7 OBE, UK. E-mail: Kuntal.Chakravarty@bhrhospitals.nhs.uk

and together will provide sufficient up-to-date knowledge about the DMARDs. This guideline also addresses many unresolved and evolving issues that can be considered as part of a research or audit, locally or nationally.

It is essential that clinicians remember to report (yellow card system) any serious adverse events (SAE) related to the use of DMARDs.

Target audience

This document is targeted at the following:

(1) Health care professionals in primary and secondary care.
(2) Health service managers.
(3) Patients receiving these drugs and patient organizations, such as Arthritis Care, and national patient support groups, such as the National Rheumatoid Arthritis Society (NRAS).
(4) Other national societies, such as the BAD.

The areas the guideline does not cover

(1) The management of DMARD therapy in children with inflammatory arthritis. The British Society for Paediatric and Adolescent Rheumatology (BSPAR) has produced guidelines [7].
(2) The management of the underlying disease for which the DMARD is prescribed.
(3) The management of RA with immunotherapies, such as anti-TNF, anti-IL-1 and anti-B-cell therapy [8].
(4) This guideline does not advise specific monitoring profile for patients receiving 'combination' therapy. Where the monitoring schedule is different between the drugs used in combination, it is advised to adopt a more stringent monitoring schedule based on clinical judgement.
(5) This guideline does not advise on the management of patients on cyclophosphamide, as this drug is more commonly used in the treatment of vasculitis and will be discussed in the guideline for the management of adults with vasculitis [9].
(6) Immunization: It is beyond the scope of this guideline to give detailed advice on immunization in patients treated with DMARDs, as there is insufficient evidence about the degree of immunosuppression induced by the drugs. However, some general principles have been mentioned. The advice on immunization, particularly against encapsulated organism, such as pneumovax, has been mentioned on the website of the Health Protection Agency. As guidelines are evolving, in difficult cases it is advisable to discuss with the Health Protection Agency, or check their website, for further advice (Prof. Liz Miller, Centre for Infectious Disease and Immunisation, Colindale, London, personal communication).

Stakeholder involvements

Names and roles of members of multidisciplinary team

Names	Representing
Prof. Kuntal Chakravarty Consultant Rheumatologist BHR Trust Hospitals Harold Wood Hospital Romford, Essex	BSR–Chairman
Dr Robert Chalmers Consultant Dermatologist Manchester Royal Infirmary Manchester	British Association of Dermatologists (Co-opted member)
Dr Harry McDonald General Practitioner Gubbins Lane Surgery Havering PCT Essex	Royal College of General Practitioners
Dr Tom Kennedy Royal Liverpool and Broadgreen University Hospital Trust Prescott Road Liverpool	BSR–Consultant Rheumatologist
Mrs Janice Mooney Lecturer/Practitioner Norfolk & Norwich University Hospital Norwich	Specialist Nurse (Rheumatology Forum)
Mrs Susan Oliver Nurse Consultant & Chairperson, Rheumatology Forum Royal College of Nursing London	Royal College of Nursing
Dr Tom Pullar Consultant Rheumatologist Ninewells Hospital Dundee	BSR–Consultant Rheumatologist
Ms Margaret Somerville Clinical Research Manager Norfolk & Norwich University Hospital Norwich	BHPR (British Health Professionals in Rheumatology)
Dr Allister Taggart Consultant Rheumatologist Musgrave Park Hospital Belfast	BSR–Consultant Rheumatologist

Names and affiliations of users on the working group

Mrs Ailsa Bosworth
Chief Executive, NRAS
National Rheumatoid Arthritis Society (NRAS)
Unit B4, Westcott Business Centre
Westcott Way, Little Wick Green
Maidenhead, SL6 3RT

Involvement of other people or organizations including user representative organizations and pharmaceutical companies in the development of the guideline

This guideline was developed in collaboration with the NRAS. Patient surveys related to DMARD treatments and the patients' perspectives have been included [10]. No representatives of pharmaceutical companies were involved in guideline development.

Rigour of development

Statement of scope of literature search and strategy employed

A comprehensive literature search was undertaken prior to the development of this guideline. Searches were conducted using MEDLINE, CINAHL, Cochrane, PUBMED, EMBASE, AMED and PsycINFO. MEDLINE is widely recognized as the premier source for bibliographic coverage of bio-medical literature and CINAHL for nursing literature. A manual search from the references cited by generated articles was also used. Search terms

used were relevant to each section of the guideline. Evidence was graded according to the strength of literature to support each statement, using the grading suggested by the Royal College of Physicians of London [11] and the document was prepared in accordance with the principles outlined in the Appraisal of Guidelines Research and Evaluation (AGREE) guidelines [12].

Statement of any limit of search

The literature search was confined to new evidence since the previous guideline was produced in 2000 and non-English literature was not reviewed.

Statement of when the guideline will be updated

It is expected that the guideline will be updated after another 5 yrs.

Guideline itself

Eligibility criteria

The eligibility of a patient to receive DMARD therapy will be at the discretion of the prescribing physician after full discussion with the patient about the potential benefits and adverse effects of the therapy. The statements made in this guideline should be considered in conjunction with the guideline on the management of RA [13].

Exclusion criteria

The prescribing physician is responsible for identifying patients who should not receive DMARD therapy. For example, many of the drugs are not suitable for people considering starting a family, and this will be discussed with each drug.

Assessment of disease and response to treatment

This is detailed in the Guideline for the Management of RA [13]. It is important to note that monitoring carried out for assessing side effects to the therapy can also be useful in monitoring treatment response.

Criteria for withdrawal of therapy

The two common reasons for withdrawal of any drug therapy are inefficacy and adverse effects of the drug and are equally applicable to all the drugs in this guideline. Temporary withdrawal is advised in some clinical circumstances if patients develop an untoward side effect or in some physiological conditions e.g. pregnancy/lactation/severe acute illness.

General principles

DMARDs are slow acting drugs which may take weeks to months to produce any clinical response. Patients need to be informed about the delayed action of these drugs and the need to persevere with the treatment (in the absence of side effect). Compliance with DMARDs therapy improves when patients follow a mutually agreed recommendation [14, 15].

Combination therapies with DMARDs may be initiated in a 'sequential step up' approach in patients not responding to monotherapy. Alternatively, 'step down' therapy may be undertaken when combination therapy was commenced in the early phase of the disease [13].

The monitoring requirements for each drug are described fully. Where monitoring requirements differ between rheumatological and dermatological conditions, the differences are clearly highlighted in the schedule for the individual drug.

The key statements when monitoring a DMARD are:

(1) In addition to absolute values for any haematological or biochemical indices, a rapid unusual fall or rise or a consistent downward or upward trend in any value should prompt caution and extra vigilance.
(2) Details of monitoring schedules should be recorded in the patients' case notes.
(3) Patients should be provided with access to the results of their monitoring. It is recommended that each patient is issued with a patient held booklet [15], however, information technology (IT) solutions may become more usual.
(4) Wherever possible, as part of a self-management programme, patients should be encouraged to take responsibility for monitoring their own therapy.
(5) The recommendations for optimal timing of monitoring are based on clinical experience, as there is little evidence to inform the optimal timing of monitoring schedules.

The following DMARDs are discussed in this document

(1) Auranofin (oral gold).
(2) Azathioprine.
(3) Ciclosporin.
(4) D-Penicillamine.
(5) Hydroxychloroquine.
(6) Leflunomide.
(7) Methotrexate.
(8) Mycophenolate mofetil (MMF).
(9) Sodium aurothiomalate.
(10) Sulfasalazine.

Applicability and utility

A statement of potential organizational barriers to introduction

These guidelines are timely as current changes in healthcare provision and monitoring have an impact on patient management.

The development of this guideline will support care of patients receiving DMARDs in both primary and secondary care, through the national programme of 'near patient testing'.

Programmes for DMARD therapy monitoring are already in existence, usually shared with primary care. It is therefore not anticipated that there will be significant organizational barriers to introduction of the recommendations detailed in this guideline.

Potential cost implications for the introduction of guideline

Significant costs will be incurred to ensure that there are robust means to act on the results of the monitoring programme. Other costs will be guideline distribution and the provision of a local means of sharing the results through patient-held booklets or IT systems.

Mechanism for the audit of guideline

Audit will be very important, as the guideline lacks good evidence in many areas. Suggested audit topics are described with each therapy.

Appendices

Working party membership, affiliations and conflicts of interest

The working party was set up independently of any input or funding from the manufacturers of the DMARDs included in the guideline. Members of the working party were asked to clarify their relationship with the pharmaceutical companies. Members were asked to declare if they, as individuals, had been sponsored to attend scientific or other meetings in the past 24 months, or if they had a direct financial stake in the manufacturing companies.

They were also asked if their units had received funding from the manufacturers to take part in clinical trials of any of the drugs in the DMARD guidelines.

Disclosure statement: K.C. has received honoraria for lecturing at GP meetings from Servier, Aventis and MSD, and is a member of the Advising Panel. S.O. has carried out consultancy work for National Patient Satefy Agency (Methotrexate) and a number of educational/advisory roles for Medac UK, Wyeth, Abbott, Schering, Plough, Pfizer and Roche. A.B. has received unrestrictive educational grants for Abbott, Schering Plough, Roche and Wyeth in the last 12 months. H.M. is a shareholder in GlaxoSmithKline and Astra Zeneca. A.T. has acted as a medical advisor to Abbott Laboratories, Merck Sharp and Dohme Ltd, Roche Pharmaceuticals, Schering Plough and Wyeth. T.P. is in receipt of a research grant from Wyeth and his unit has a nurse specialist jointly funded by Abbott and Wyeth. All other authors have declared no conflicts of interest.

References with indication of level of evidence

The guidelines are referenced and graded according to the AGREE and Royal College of Physicians concise guidance to good practice [11, 12].

A = Evidence from at least one properly performed, randomized controlled trial or meta-analysis of several controlled trials.

B = Well-conducted clinical studies, but no randomized clinical trials; evidence may be extensive but essentially descriptive.

C = Evidence obtained from expert committee reports or opinions, and/or clinical experience of respected authorities. This grading indicates an absence of directly applicable studies of good quality.

Summary

DMARDs

DMARDs are fundamental to arresting the disease process in RA and other inflammatory arthritides. Many are also used for other licensed and unlicensed indications, such as chronic inflammatory skin or bowel disease. While early initiation of therapy is essential to arrest RA, sustained use is vital if disease suppression is to be maintained, and so these drugs may be used for an unlimited period of time. Prolonged therapy requires long-term monitoring for toxicity and safety profile.

Whatever DMARD is considered appropriate for a patient, it is paramount that the patient is carefully monitored so that there is no delay in the detection of any untoward effect of the drug. Monitoring will also contribute to assessing activity of the underlying disease.

References

1 Grigor C, Capell H, Stirling A *et al.* Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263–9.
2 Wolfe F, Cush JJ, O'Dell JR *et al.* Consensus recommendations for the assessment and treatment of rheumatoid arthritis. J Rheumatol 2001;28:1423–30.
3 British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary.
4 Kay AG. Myelotoxicity of gold. Br Med J 1976;1:1266–8.
5 Kay AG. Myelotoxicity of D-penicillamine. Ann Rheum Dis 1979;38:232–6.
6 Wright V, Amos R. Do drugs change the course of rheumatoid arthritis? Br Med J 1980;280:964–6.
7 British Society of Paediatric & Adolescent Rheumatology (BSPAR). www.bspar.org.uk/
8 Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNFα blockers in adults with rheumatoid arthritis. Rheumatology 2005;44:157–63.
9 Lapraik C, Watts R, Bacon P *et al.* BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. Rheumatology 2007;46:1615–6.
10 Bosworth A. National Rheumatoid Arthritis Society Survey 2005. Disease modifying anti-rheumatic drugs and biologics. www.rheumatoid.org.uk
11 Royal College of Physicians Concise guidance to good practice, 2003. www.rcplondon.ac.uk/college/ceeu/ConciseGuidelineDevelopmentNotes.pdf
12 Appraisal of Guidelines for research & evaluation – AGREE Collaboration, 2001. www.agreecollaboration.org
13 Luqmani R, Hennell S, Estrach C *et al.* British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the Management of Rheumatoid Arthritis (the first two years). Rheumatology 2006;45:1167–9.
14 Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. J Clin Pharm Ther 2001;26:331–42.
15 Patient Held Booklet – 2006 NPSA. http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/oral-methotrexate/ (15 February 2008, date last accessed).

Auranofin

A. Indications: (Licensed) Adult rheumatoid arthritis
BAD: Dermatologists generally do not use this drug.

B. Dose: Grade of evidence: C
Typical dose: 3 mg 2–3 times daily.

C. Route of administration: Oral

D. Time to response: 4–6 months [1–5]

E. Caution: Grade of evidence: C
Elderly, moderate renal or hepatic impairment, history of urticaria, eczema or inflammatory bowel disease [3, 4].

F. Contraindications: Grade of evidence: C

(1) Severe renal or hepatic impairment.
(2) History of blood disorders or marrow aplasia, exfoliative dermatitis.
(3) Systemic lupus erythematosus.
(4) Necrotising enterocolitis.
(5) Significant pulmonary fibrosis [3].
(6) Porphyria [4].
(7) Pregnancy and lactation [2–4].

G. Monitoring schedule: Grade of evidence: C

	BSR
(a) Pre-treatment assessment	FBC, urinalysis, U&E, LFTs [1, 2, 4]
(b) Monitoring	FBC and urinalysis every 4 weeks [1, 2, 4, 5] Patient should be asked about the presence of any skin rash or oral ulceration at each visit.

FBC: full blood count; U&E: urea and electrolytes; LFT: liver function test.

H. Actions to be taken: Grade of evidence: C

WBC $< 3.5 \times 10^9$/l [1, 2]	Withhold until discussed with specialist team.
Neutropaenia $< 2.0 \times 10^9$/l [1, 2]	Withhold until discussed with specialist team.
Eosinophilia $> 0.5 \times 10^9$/l	Caution and increased vigilance required.
Platelets $< 150 \times 10^9$/l [1, 2]	Withhold until discussed with specialist team.
If proteinuria is 2+ or more [1, 2]	Check MSSU: If evidence of infection treat appropriately. If sterile and 2+ proteinuria or more persists, withhold until discussed with specialist team.
Rash (usually itchy) or oral ulceration [1, 2]	Withhold until discussed with specialist team.
Abnormal bruising or severe sore throat [1, 2]	Check FBC immediately and withhold until results are available.

MSSU: mid-stream specimen urine.

References

Auranofin

1 White CE, Cooper RG. Prescribing and monitoring of disease-modifying anti-rheumatic drugs (DMARDs) for inflammatory arthritis. In: Collected reports on the

rheumatic diseases 2005. Arthritis Research Campaign. Available at: http://www.arc.org.uk/arthinfo/documents/6508.pdf
2 British Society of Rheumatology. National guidelines for monitoring of second line drugs, 2000. www.rheumatology.org.uk/
3 British National Formulary 48. Pharmaceutical Press, 2004.
4 Summary of Product Characteristics Auranofin Middlesex, UK: Astellas Pharma Ltd, 2006.
5 American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum 2002;46:328–46.

Azathioprine

A. Indications: (Licensed) RA, dermatomyositis and polymyositis, autoimmune and chronic active hepatitis, pemphigus vulgaris. (Unlicensed) Vasculitides, such as polyarteritis and giant cell arteritis [1] and systemic lupus erythematosus, psoriasis and psoriatic arthritis, severe eczema, bullous dermatoses including pemphigoid, inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease.

B. Dose: Grade of evidence: B
Typical dose: 1 mg/kg/day—increasing after 4–6 weeks to 2–3 mg/kg/day.

C. Route of administration: Oral or intravenous—The latter is very irritant and should be used only if oral route is not feasible. (The intravenous route is hardly ever used in rheumatology.)

D. Time to response: 6 weeks to 3 months

E. Cautions: Grade of evidence: C

(1) Thiopurine methyl transferase (TPMT) deficiency (heterozygous state): May be associated with delayed haematotoxicity including bone marrow toxicity. Please see section subsequently on TPMT [2].
(2) Sunscreens and protective covering should be encouraged to reduce sunlight exposure [3].
(3) Localized or systemic infection including hepatitis B or C and history of tuberculosis.

F. Contraindications: Grade of evidence: C

(1) Immunization with live vaccines (see section J1).
(2) Pregnancy and breast feeding except in clinically indicated cases (see section on pregnancy) (see section J2).
(3) TPMT deficiency (homozygous state): Avoid, can be fatal (see section J3) [2].
(4) Individuals with Lesch-Nyhan Syndrome → due to congenital hypoxanthine-guanine phosphoribosyl transferase (HGPRT) deficiency.

G. Notable drug interactions (refer to BNF and SPC)

(1) Allopurinol: Azathioprine dose should be reduced to 25% of the original dose [4].
(2) Warfarin: Azathioprine inhibits the anticoagulant effects of warfarin [4–6]. Alternatively, consider increasing the dose of warfarin.
(3) Phenytoin, sodium valproate, carbamazepine: Azathioprine reduces the absorption of these drugs.
(4) Angiotensin-converting enzyme (ACE) inhibitors: Co-prescription of azathioprine may cause anaemia [3, 4] (if significant, consider alternative to ACE inhibitor or different DMARD).
(5) Aminosalicylates i.e. mesalazine, olsalazine, balsalazide or sulfasalazine, may contribute to bone marrow toxicity.
(6) Co-trimoxazole and trimethoprim can cause life threatening haematoxicity [3, 4].

H. Monitoring schedule: Grade of evidence: C

	BSR	BAD
(a) Pre-treatment assessment	FBC, U&E, creatinine, LFTs, and TPMT assay.	Same as BSR.
(b) Monitoring	FBC and LFT's weekly for 6 weeks and continue every 2 weeks until dose stable for 6 weeks; then monthly.	FBC, LFT weekly until stable on maintenance dose.
	If maintenance dose is achieved and stable for 6 months consider discussing with patient to reduce monitoring to 3 monthly.	Same as BSR.
	In people heterozygote for TPMT, monitoring should continue at monthly intervals at minimum (see section J3).	Same as BSR.
(c) Following changes in dose	Repeat FBC and LFT's 2 weeks after dose change and then monthly.	Same as BSR.
(d) Regular review	U&E and creatinine should be repeated 6 monthly.	Same as BSR.

I. Actions to be taken: Grade of evidence: B

WBC $< 3.5 \times 10^9$/l	Withhold until discussed with specialist team.
Neutrophils $< 2.0 \times 10^9$/l	Withhold until discussed with specialist team.
Platelets $< 150 \times 10^9$/l	Withhold until discussed with specialist team.
AST, ALT > twice upper limit of normal	Withhold until discussed with specialist team.
Rash or oral ulceration	Withhold until discussed with specialist team.
MCV > 105 fl	Check serum folate and B12 & TSH. Treat any underlying abnormality. If results normal discuss with specialist team.
Abnormal bruising or severe sore throat	Withhold until FBC results available and discuss with the specialist team.

MCV: mean corpuscular volume; TSH: thyroid-stimulating hormone.

J. Caveats:

(1) Immunization [7]:
  (a) Patients receiving azathioprine must not receive immunization with live vaccines. Inactivated polio is available although suboptimal response may be seen.
  (b) Annual flu vaccination is recommended.
  (c) In patients receiving azathioprine exposed to chickenpox or shingles, passive immunization should be carried out using varicella zoster immunoglobulin (VZIG).
(2) Pregnancy and breast feeding:
  (a) Women of childbearing potential should be advised to use effective contraceptive precautions. Evidence of mutagenicity is equivocal in men. In most cases, azathioprine should not be prescribed if there is a possibility of pregnancy, although there may be some circumstances where the benefit of continuing treatment outweighs the possible risks related to the unborn child. A careful assessment of risk *vs* benefit is advised. Dose reduction at 32 weeks of gestation may prevent neonatal leucopenia.
  (b) Women treated with azathioprine should not breast feed [3, 4, 8, 9].
(3) TPMT assay: This assay provides additional information of risks related to treatment but does not replace routine monitoring [10, 11]. However, for those with higher levels of serum TPMT, higher doses of azathioprine may be required. Homozygous deficiency is associated with serious and fatal toxicity that may occur within 6 weeks of starting azathioprine [11].
Heterozygous deficiency is also linked to serious adverse events, although the symptoms may not be evident until

6 months after commencing treatment. Minor unrecognized infections or drug interactions, particularly when co-prescribed with aminosalicylates, such as sulfasalazine, mesalazine or olsalazine, may precipitate fatal toxicity. Heterozygous individuals should be prescribed azathioprine with caution and, in particular, reduced drug dosage.

K. Unresolved and evolving issues:
These issues could be considered for future randomized clinical trials or audits locally, regionally or nationally.

(1) Role of TPMT in predicting haemato-toxicity in rheumatological diseases?
(2) Is there any relationship of azathioprine and skin or cervical cancer?
(3) The safety of azathioprine in pregnancy?
(4) Is there any association between azathioprine and pancreatitis?

References

Azathioprine

1 Paice EW. Giant cell arteritis: difficult decisions in diagnosis, investigation and treatment. Postgrad Med J 1989;65:743–7.
2 Konstantopoulou M, Belgi A, Griffiths KD, Seale JR, Macfarlane AW. Azathioprine-induced pancytopenia in a patient with pompholyx and deficiency of erythrocyte thiopurine methyltransferase. Br Med J 2005;330:350–1.
3 Imuran Summary of product characteristics 25 & 50mg: 23 July and 5 August, Glaxo Smith Kline. http://emc.medicines.org.uk
4 British National Formulary 54. Pharmaceutical Press, 2007.
5 Cronstein BN. Pharmacogenetics in the rheumatic diseases. Ann Rheum Dis 2004;63(Supp. 2):ii25–7.
6 Rivier G, Khamashta MA, Hughes GR. Warfarin and azathioprine: a drug interaction does exist. Am J Med 1993;95:342.
7 Jenner E. Immunisation against infectious disease. Bicentenary Edition 1996. Her Majesty's Stationary Office, Department of Health, London UK. www.dh.gov.uk/
8 Ramsey-Goldman R. Treatment of inflammatory rheumatic disorders in pregnancy: what are the safest treatment options? Drug Saf 1998;19:389–410.
9 Ostensen M. Disease Specific problems related to drug therapy in pregnancy. Lupus 2004;13:746–50.
10 Clunie GPR, Lennard L. Relevance of thiopurine methyltransferase status in rheumatology patients receiving azathioprine. Rheumatology 2004;43:13–8.
11 Tavadia SMB, Mydlarski PR, Reis MD *et al.* Screening for azathioprine toxicity: a pharmacoeconomic analysis based on a target case. J Am Acad Dermatol 2000;42:628–32.

Ciclosporin

A. Indications: (Licensed) RA, psoriasis and atopic dermatitis

B. Dose: Grade of evidence: C

(1) RA starting dose: 2.5 mg/kg/day in two divided doses for 6 weeks and then may be increased at 2–4 weeks intervals by 25 mg until clinically effective or the maximum dose of 4 mg/kg/day is reached [1–3].
Maintenance dose: Often effective between 2.5–3.2 mg/kg/day. Adjust to patient's tolerance and benefit. Constantly evaluate response and toxicity before increasing to the maximum dose.
Maximum dose: 4 mg/kg/day [1–3].
(2) Psoriasis and atopic dermatitis (BAD): starting dose 2.5–5 mg/kg/day depending on disease severity and then treated according to response; maximum dose 5 mg/kg/day.

C. Route of administration: Oral

D. Time to response: 3 months; If NO clinical response at maximum tolerated dose for 3 months, then withdraw the treatment [3, 4].

E. Cautions: Grade of evidence: A & C

(1) Pregnancy and lactation [5, 6].
(2) Grapefruit including grapefruit juice must be avoided for 1 h before or after taking ciclosporin tablets as bioavailability is increased [2].
(3) Malignancy such as lymphomas, etc [4, 6].

F. Contraindications: Grade of evidence: C

(1) Uncontrolled hypertension [1, 4, 6–8].
(2) Renal and liver failure (in patients with RA) [6].
(3) Severe electrolyte imbalance i.e. hyperkalemia [1, 2].
(4) Suspected systemic infection or sepsis [6].

G. Notable drug interaction (refer to BNF and SPC)

(1) Diclofenac: Reduce the dose of diclofenac by 50% [1–3]
(2) Colchicine: To be avoided [1, 2].
(3) Simvastatin: maximum dose 10 mg/day [6].
(4) Nifedipine: use with caution [6].
(5) Digoxin: May increase the serum levels of digoxin [6].
(6) St. John's Wort: decreases ciclosporin activity [6].
(7) Potassium sparing diuretics.

H. Monitoring schedule: Grade of evidence: C

	BSR and BAD
(a) Pre-treatment assessment	FBC incl. differential white cell count, U&E, creatinine: (check twice, 2 weeks apart, to obtain a mean value for creatinine), LFT, fasting lipids, creatinine clearance prior to starting the drug. Blood pressure: to be $\leq$140/90 before treatment on two measurements 2 weeks apart [8]. If greater than this treat hypertension before starting ciclosporin. In patients with psoriatic arthritis: Assess whether patient has received PUVA before commencing ciclosporin. If total dose exceeds 1000 J discuss with dermatologists.
(b) Monitoring	FBC & LFT: once a month until dose and trend stable for 3 months and then 3 monthly. Serum electrolytes incl. potassium and creatinine every 2 weeks until dose and trend stable for 3 months and then monthly. Watch when NSAID is added, particularly diclofenac. Check fasting lipids periodically [3]. Blood pressure (BP): Check BP each time patient attends monitoring clinic and maintain $\leq$140/90.

I. Actions to be taken: Grade of evidence: C

Creatinine rises >30% from baseline	Repeat in 1 week and if still >30% above baseline withhold until discussed with the specialist team.
Potassium rises to above the reference range	Withhold until discussed with the specialist team.
Platelets $<150 \times 10^9$/l	Withhold until discussed with the specialist team.
'Significant' rise in fasting lipids	Withhold until discussed with the specialist team.
High BP: $\geq$140/90 on two consecutive readings 2 weeks apart	Treat blood pressure before stopping the ciclosporin (note interactions with several anti-hypertensives). If BP cannot be controlled, stop ciclosporin and obtain BP control before restarting ciclosporin. Discuss with the specialist team.
AST, ALT or alkaline phosphatase more than 2× upper limit of reference range	Withhold until discussed with the specialist team. Check any other reason such as alcohol, drug interaction including over the counter medication.
Abnormal bruising	Check FBC immediately and withhold until discussed with the specialist team.

AST: aspartate aminotransferase; ALT: alanine aminotransferase.

J. Immunization:

(1) Patients receiving ciclosporin must not receive immunization with live vaccines. Inactivated polio is available although suboptimal response may be seen.

(2) Annual flu vaccination is recommended.
(3) In patients receiving ciclosporin exposed to chickenpox or shingles, passive immunization should be carried out using VZIG.

K. Unresolved and evolving issues:
The role of magnesium monitoring in people with RA treated with ciclosporin requires evaluation.

References

Ciclosporin

1 British Society for Rheumatology. National Guidelines for the monitoring of second line drugs, 2000. www.rheumatology.org.uk/
2 British National Formulary 52. Pharmaceutical Press, 2006.
3 Summary of Product Characteristics from Novartis as makers of Neoral, (in respect of Rheumatoid Disease). Novartis Pharmaceuticals UK Ltd, Surrey, UK. http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentID=1307 (17 October 2007, date last accessed).
4 Neoral Label information http://www.fda.gov/cder/foi/label/2002/50715s10s14lbl.pdf (24 October 2007, date last accessed).
5 Dijkmans BA. Safety aspects of ciclosporin in rheumatoid arthritis. Drugs 1995;50(suppl. 1):41–7.
6 Adverse Drug Reactions Information Service, Yellow Card Data, 2004.
7 Flipo RM, Cortet B, Duquesne B, Delacambre B. Cyclosporin-A in refractory rheumatoid arthritis. Rev Med Interne 1994;15:166–73.
8 Hypertension: management of hypertension in adults in primary care, 2006. http://www.nice.org.uk/guidance/CG34/guidance/pdf/English (15th February 2008, date last accessed).

D-Penicillamine

A. Indications: (Licensed) RA and Wilson's disease
BAD: Dermatologists generally do not use this drug.

B. Dose: Grade of evidence: A
Typical regimen: 125–250 mg/day increasing by 125 mg every 4 weeks to 500 mg/day [1–5]. If no response in 3 months consider an increase in dose to 750 mg/day.
Maximum dose is 1–1.5 g/day [4, 5] but there appears to be no clear advantage in using doses greater than 500 mg/day [1, 6].
Inadequate response to 750 mg/day should prompt a review of the patient's DMARD therapy [2, 4].

C. Route of administration: Oral

D. Time to response: 3–6 months [3–7]

E. Caution: Grade of evidence: C
Renal impairment, concomitant nephrotoxic drugs including gold treatment [5].

F. Contraindications: Grade of evidence: C

(1) Systemic lupus erythematosus.
(2) Renal impairment (moderate to severe) [4, 5].
(3) Pregnancy and lactation: Avoid [4, 5].

G. Notable drug interactions:

(1) Antacids, iron or zinc supplements: Do not give within 2 h as D-penicillamine absorption is reduced.
(2) Antipsychotic drugs: May increase risk of agranulocytosis.
(3) Digoxin: Levels of digoxin can be reduced by concurrent use of D-Penicillamine.

H. Monitoring schedule: Grade of evidence: C

	BSR
(a) Pre-treatment assessment	FBC, U&E, creatinine and urinary dipstick for protein.
(b) Monitoring	FBC and urinalysis every 2 weeks until dose stable for 3 months and then monthly [2, 3]. Patient should be asked about the presence of rash or oral ulceration at each visit.

I. Actions to be taken: Grade of evidence: C

WBC $< 3.5 \times 10^9$/l [2, 7]	Withhold until discussed with specialist team.
Neutrophils $< 2.0 \times 10^9$/l [2, 7]	Withhold until discussed with specialist team.
Platelets $< 150 \times 10^9$/l [2, 7]	Withhold until discussed with specialist team.
If proteinuria is 2+ or more [2, 7]	Check MSSU: If evidence of infection treat appropriately. If sterile and 2+ proteinuria or more persists, withhold until discussed with specialist team.
Severe rash or oral ulceration [2, 7]. Late rashes are more serious than early ones [4, 5].	Withhold until discussed with specialist team.
Nausea	Taking medication before bed may reduce nausea.
Alteration of taste [2, 7]	Continue treatment (may settle spontaneously).
Abnormal bruising or severe sore throat [2, 7]	Check FBC immediately and withhold until results are available.

References

D-Penicillamine

1 Suarez-Almazor ME, Spooner C, Belseck E. Penicillamine for treating rheumatoid arthritis. Cochrane Database Syst Rev 2000;4:CD001460.
2 British Society for Rheumatology. National guidelines for the monitoring of second line drugs, 2000. www.rheumatology.org.uk/
3 American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum 2002;46:328–46.
4 British National Formulary 48. Pharmaceutical Press, 2004.
5 Summary of product characteristics from Alliance Pharmaceuticals as makers of Distamine. 26 October 2004.
6 Dixon AJ, Davies J, Dormandy TL *et al.* Synthetic D(-)penicillamine in rheumatoid arthritis. Double-blind controlled study of a high and low dosage regimen. Ann Rheum Dis 1975;34:416–21.
7 White CE, Cooper RG. Prescribing and monitoring of disease-modifying anti-rheumatic drugs (DMARDs) for inflammatory arthritis. In: collected reports on the rheumatic diseases 2005. Arthritis Research Campaign. Available at: http://www.arc.org.uk/arthinfo/documents/6508.pdf

Hydroxychloroquine

A. Indications: (Licensed) RA, connective tissue diseases (systemic and discoid lupus) and some photosensitive dermatological conditions

B. Dose: Grade of evidence: C
Typical regime: 200–400 mg daily. Dosage may be reduced to 200 mg daily depending on clinical response.
Maximum dose: Should not exceed 6.5 mg/kg body weight per day [1–5].

C. Route of administration: Oral

D. Caution: Grade of evidence: C

(1) Patients with renal and liver impairment [4].
(2) Patients with epilepsy: may reduce threshold for convulsions [4].
(3) Avoid antacids within 4 h of dose [4].
(4) May exacerbate psoriasis [3].

E. Contraindications: Grade of evidence: C

(1) Breast feeding (see section G).
(2) Pre-existing maculopathy [4].

F. Notable drug interactions (refer to BNF and SPC)

(1) Digoxin: Concomitant administration may cause an increase in plasma concentration of digoxin [4].
(2) Methotrexate: Concomitant administration may increase plasma concentration of methotrexate although

methotrexate and hydroxychloroquine are often used in combination.
(3) Ciclosporin: Concomitant administration may increase plasma concentration of ciclosporin.
(4) Known hypersensitivity to 4-aminoquinoline compounds [3].
(5) Avoid use with amiodorone, moxifloxacin and quinine [4].
(6) Avoid concomitant use of mefloquine [4].

G. Pregnancy and breast feeding: Category of evidence: B

(1) Hydroxychloroquine has been used relatively safely in pregnancy [4, 6–13]. The risks of stopping treatment should be weighed against the small possible risk to the unborn child [6–13].
(2) Breast feeding is contraindicated.

H. Monitoring schedule: Grade of evidence: B

	BSR and BAD
(a) Pre-treatment assessment	FBC, U&E, LFT. Ask about visual impairment which is not corrected by glasses [1]. Record near visual acuity of each eye (with reading glasses if worn) using a test type—or the reading chart [1]. If no abnormality detected, commence treatment. If an abnormality detected refer first to an optometrist.
(b) Monitoring	The Royal College of Ophthalmologists (RCO) recommend (1): Annual review either by an optometrist or enquiring about visual symptoms, rechecking visual acuity and assessing for blurred vision using the reading chart. Patients should be advised to report any visual disturbance [1, 14, 15].

I. Actions to be taken: Grade of evidence: B
Reproduced with kind permission from the RCO: Ocular toxicity and hydroxychloroquine: Guidelines for screening 2004.

Visual impairment detected at baseline	Refer to optometrist and then if appropriate to ophthalmologist
Development of blurred vision or changes in visual acuity	Stop medication and then, as above
Patients requiring long-term therapy (5 yrs)	Discuss with ophthalmologist

J. Unresolved and evolving issues
Research/survey or audit on safety of hydroxychloroquine use during breast feeding can be undertaken.

References

Hydroxychloroquine

1 The Royal College of Ophthalmologists. Ocular Toxicity and Hydroxychloroquine: Guidelines for Screening 2004. www.rcophth.ac.uk/
2 Mackenzie AH. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. Am J Med 1983;75:40–5.
3 Plaquenil. Summary of product characteristics. Sanofi Synthelabo, 2003.
4 British National Formulary 47. Pharmaceutical Press, 2004.
5 Grierson DJ. Hydroxychloroquine and visual screening in a rheumatology outpatient clinic. Ann Rheum Dis 1997;56:188–90.
6 Canadian Rheumatology Association. Canadian Consensus Conference on Hydroxychloroquine. J Rheumatol 2000;27:2919–21.
7 Buchanan NM, Toubi E, Khamashta MA, Lima F, Kerslake S, Hughes GR. Hydroxychloroquine and lupus pregnancy: review of a series of 36 cases. Ann Rheum Dis 1996;55:486–8.
8 Parke A. Antimalarial drugs and pregnancy. Am J Med 1988;85(Suppl 4A):30–3.
9 Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. Arch Intern Med 2000;160:610–9.
10 Klinger G, Morad Y, Westall CA *et al.* Ocular toxicity and antenatal exposure to chloroquine or hydroxychloroquine for rheumatic diseases. Lancet 2001;358:813–4.
11 Oslensen M. Disease specific problems related to drug therapy in pregnancy. Lupus 2004;13:746–50.
12 Costedoat-Chalumeau N, Amoura Z, Duhaut P *et al.* Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. Arthritis Rheum 2003;48:3207–11.
13 Costedoat-Chalumeau N, Amoura Z, Huong DL, Lechat P, Piette JC. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases. Review of the literature. Autoimmun Rev 2005;4:111–5.
14 Mavrikakis I, Sfikakis PP, Mavrikakis E *et al.* The incidence of irreversible retinal toxicity in patients treated with hydroxychloroquine- a reappraisal. Ophthalmology 2003;110:1321–6.
15 Silman A, Shipley M. Ophthalmological monitoring for hydroxychloroquine toxicity: a scientific review of available data. Br J Rheumatol 1997; 36:599–601.

Leflunomide

A. Indications: (Licensed) RA and psoriatic arthritis (PsA). Not used in Psoriasis.
BAD: Dermatologists generally do not use this drug.

B. Dose: Grade of evidence: C
Typical dose is:
RA: 10–20 mg once a day [1–3] when monotherapy is used. In cases of combination therapy with another potentially hepatotoxic DMARD like methotrexate, 10 mg once a day is recommended (therapeutic efficacy may be reduced with the reduced dosage [4]).
PsA: 20 mg once a day [2, 3].

Loading dose: 100 mg once daily for 3 days [2, 3] may be used to speed up the onset of effect. Unacceptable gastrointestinal (GI) side effects such as diarrhoea may occur when a loading dose is given and this is often omitted in routine practice [5]. A loading dose is not recommended when used as part of combination therapy.

C. Route of administration: Oral

D. Time to response: 8–12 weeks (longer if loading dose is not employed)

E. Caution: Grade of evidence: A & C [2, 3, 6–9]

(1) Localized or systemic infection including hepatitis B or C and history of tuberculosis.
(2) Drug potentiation: Haematotoxic or hepatotoxic drugs such as methotrexate. Leflunomide SPC states caution if used together with methotrexate although combination therapy using these drugs has been used [10].

F. Contraindications: Grade of evidence: C [1, 2, 5]

(1) Severe immunodeficiency.
(2) Serious infections.
(3) Impaired liver function due to any cause.
(4) Severe unexplained hypoproteinaemia.
(5) Renal impairment (moderate to severe).
(6) Impairment of bone marrow function as indicated by anaemia and cytopenias due to causes other than RA and PsA.

G. Monitoring schedule: Grade of evidence: C [1, 2]

	BSR
(a) Pre-treatment assessment	FBC, U&E's creatinine and LFTs [2].
	Blood pressure: If >140/90 on two consecutive readings 2 weeks apart treat hypertension before commencing the drug [9, 11].
	Weight: to allow assessment of weight loss: this may be attributable to leflunomide.
(b) Monitoring	FBC, LFTs every month for 6 months and, if stable, 2 monthly thereafter [2].
	Blood checks should be continued long-term, at least once a month, if co-prescribed with another immunosuppressant or potentially hepatotoxic agent [8].
	Blood pressure and weight should be checked at each monitoring visit.

H. Action to be taken: Grade of evidence: C [5]

WBC $<3.5 \times 10^9$/l	Withhold until discussed with specialist team.
Neutrophils $<2.0 \times 10^9$/l	Withhold until discussed with specialist team.
Platelets $<150 \times 10^9$/l	Withhold until discussed with specialist team.
AST, ALT between two and three times the upper limit of reference range	If the current dose is more than 10 mg daily reduce the dose to 10 mg daily and recheck weekly until normalized. If the AST & ALT is returning to normal, leave on 10 mg a day. If LFTs remain elevated withdraw the drug and discuss with the specialist team.
AST, ALT more than three times the upper limit of reference range	Recheck LFTs within 72 h, if still more than three times the reference range, stop drug and consider washout (see section J).
Rash or itch	Consider dosage reduction with or without anti-histamines; if severe, stop and consider washout (see section J).
Hair loss	Consider dosage reduction; if severe, stop and consider washout (see section J).
Abnormal bruising or severe sore throat	Check FBC immediately and withhold until results are available.
Hypertension	If BP >140/90 treat in line with NICE guidance. If BP remains uncontrolled, stop leflunomide and consider washout (see section J).
Headache	If severe, consider dosage reduction. If headaches persist, stop and consider washout (see section J).
GI upset (nausea, diarrhoea)	If loading dose has been used, give symptomatic treatment. If steady state has been reached, give symptomatic treatment and consider dosage reduction. If symptoms are severe or persistent, stop and consider washout (see section J).
Weight loss	Monitor carefully. If >10% weight loss with no other cause identified, reduce dosage or stop and consider washout (see section J).
Breathlessness	If increasing shortness of breath occurs, stop leflunomide and consider washout (see section J).

NICE: National Institute for Health and Clinical Excellence.

NB. Simple dose reduction is unlikely to produce a rapid diminution of adverse effects as the half-life of the drug is 2 weeks (1–4 weeks). If a rapid response is required, consider washout—see section J.

I. Caveats

(1) Immunization

(a) Patients receiving leflunomide must not receive immunization with live vaccines. Inactivated polio is available although suboptimal response may be seen.
(b) Annual flu vaccination is recommended.
(c) In patients receiving leflunomide exposed to chickenpox or shingles, passive immunisation should be carried out using VZIG.

(2) Pregnancy and lactation: Leflunomide is teratogenic and must not be given to pregnant women or women of child bearing potential unless reliable contraception is used. Women planning to have children should either discontinue the drug 2 yrs prior to conception [2, 3] or have a rapid removal of its active metabolite by following the washout procedure. Men should use effective contraception for 3 months after stopping leflunomide [3].

(a) Blood concentrations should be checked prior to planned pregnancy especially if within 2 years of stopping leflunomide or following wash out [2, 3]. Any pregnancy within 2 yrs of discontinuation of leflunomide should be discussed with rheumatologist if drug washout has not been performed [2, 3]. Notify pharmaceutical company in the event of pregnancy while on leflunomide [3].
(b) Breast feeding should be avoided as animal studies indicate that metabolites of leflunomide are secreted in the breast milk [2].

(3) Hepatic toxicity: Leflunomide is a potentially hepatotoxic drug and caution is advised when using leflunomide concomitantly with another hepatotoxic drug, such as methotrexate, or if there is evidence of current or recent hepatitis with Hepatitis B or C viruses [3, 4, 6–9]. Rare cases of severe liver injury (some with fatal outcome) have been reported during treatment with leflunomide. Most cases occurred within 6 months and in a setting of multiple risk factors for hepatotoxicity [9, 10]. It is highly recommended that LFTs be monitored closely (at least once a month) if leflunomide is co-prescribed with potentially hepatotoxic drugs, such as methotrexate [5, 9, 10]. Patient should be asked to limit alcohol intake well within national limits 4–8 units a week (National Survey data 2005).

(4) Drug interactions: Leflunomide can interact with many drugs, particularly with phenytoin, tolbutamide and may enhance the effects of these drugs [1–3] although significant interaction is unlikely [5]. Leflunomide also interacts with warfarin and the International normal ratio (INR) should be very closely monitored for several weeks even after stopping the leflunomide. As leflunomide has an extremely long half-life (2 weeks) the interactions can potentially be serious and more actions may be required beside just discontinuation of the drug such as washout. This may be of practical importance when changing from leflunomide to another DMARD.

(5) GI effects: Diarrhoea often occurs early in therapy when full loading doses of 100 mg/day for 3 days are given. Such effects lead to patient dissatisfaction and issues related to compliance and subsequent withdrawal of the drug in some circumstances. Omission of loading dose is acceptable with the knowledge that there may be a slight delay in response time.

(6) Hypertension: Regular monitoring of blood pressure is necessary during treatment and if there is a significant rise in blood pressure, then this should be treated. However, it is important to undertake a risk – benefit assessment at all times. In severe uncontrolled cases it is necessary to consider stopping the drug and washout if necessary.

(7) Infections: Any infection should be treated on its own merit. All types of infection can occur and a cautious vigilance is necessary to detect early evidence of infection.

(8) Pulmonary infiltration/pneumonitis/reactions: Pulmonary infiltration/pneumonitis as an acute allergic reaction has been described in a small number of patients after starting leflunomide [12–16]. Patients should be made aware of this rare complication (see drug SPC) and if they become short of breath they should stop the tablets at once and seek

urgent medical advice. If combination therapy is used with methotrexate, the patient should be made aware of the possible added risk even though this may not be clinically significant (Dr Clive Kelly, Gateshead Hospital, personal communication).

J. Washout procedure: Grade of evidence: C
To aid drug elimination in cases of serious adverse effect or before conception, stop treatment and give either cholestyramine 8 g three times daily for 11 days or activated charcoal 50 g four times daily for 11 days; the concentration of active metabolite after washout should be less than 20 μg/l (measured on two occasions 14 days apart) in men and women before conception (consult product literature).

References

Leflunomide

1 British Society for Rheumatology. National guidelines for the monitoring of second line drugs, 2000. www.rheumatology.org.uk
2 Sanofi-aventis summary of Product characteristics http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentID=7480 (24 October 2007, date last accessed).
3 British National Formulary 48. Pharmaceutical Press, 2004.
4 Scott DL, Smolen JS, Kalden JR *et al.* Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. Ann Rheum Dis 2001;60:913–23.
5 Kalden JR, Schattenkirchner M, Sörensen H *et al.* The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: a five-year followup study. Arthritis Rheum 2003;48:1513–20.
6 Emery P, Cannon G, Holden W, Smolen J, Strand V, Schiff M. Results from a cohort of over 40,000 rheumatoid arthritis (RA) patients: adverse event (AE) profiles of leflunomide (LEF), methotrexate (MTX) and other disease-modifying antirheumatic drugs (DMARDs). Ann Rheum Dis 2002;61(Suppl. 1):42.
7 Emery P, Smolen J. Issues in rheumatoid arthritis. Lancet 1999;353:1186.
8 PSUR Periodic Safety Update Reports 6 monthly reviewers of all world wide spontaneous adverse events reports, 2004.
9 Dougados M, Emery P, Lemmel EM *et al.* Efficacy and Safety of leflunomide and predisposing factors for treatment response in patients with active rheumatoid arthritis: RELIEF 6-month data. J Rheumatol 2003;30:2572–9.
10 Dendooven A, De Rycke L, Verhelst X, Mielants H, Veys EM, De Keyser F. Leflunomide and methotrexate combination therapy in daily clinical practice. Ann Rheum Dis 2006;65:833–4.
11 Hypertension: management of hypertension in adults in primary care, 2006. http://www.nice.org.uk/guidance/CG34/guidance/pdf/English (15th February 2008, date late accessed).
12 Saravanan V, Kelly C. Drug-related pulmonary problems in patients with rheumatoid arthritis. Rheumatology 2006;45:787–9.
13 Ito S, Sumida T. Interstitial lung disease associated with leflunomide. Intern Med 2004;43:1103–4.
14 Kamata Y, Nara H, Kamimura T *et al.* Rheumatoid arthritis complicated with acute interstitial pneumonia induced by leflunomide as an adverse reaction. Intern Med 2004;43:1201–4.
15 McCurry J. Japan deaths spark concerns over arthritis drug. Lancet 2004;363:461.
16 Takeishi M, Akiyama Y, Akiba H, Adachi D, Hirano M, Mimura T. Leflunomide induced acute interstitial pneumonia. J Rheumatol 2005;32:1160–3.

Methotrexate

A. Indications: (Licensed) RA [1, 2], Psoriasis.
(Unlicensed) Psoriatic arthritis [3], Crohn's disease [4], connective tissue disease (SLE, myositis and vasculitis) [5], Felty's syndrome [6].

B1. Methotrexate dosage: Grade of evidence: C
Typical dose: 7.5–25 mg ONCE weekly; starting dose may vary depending on the severity of the condition and patient characteristics such as age, renal function and other comorbid conditions. The initial dose may be 5–10 mg once weekly, increasing by 2.5–5 mg every 2–6 weeks until disease stabilized [7]. The maximum licensed dose in RA is 25 mg/week. Rarely, the maximum dose can be 30 mg/week [8]. Lower doses should be considered for frail elderly patients who often have poor renal function. If maximum oral dose is not effective or causes intolerance, consider i.m. or subcutaneous route of administration before discontinuation of the drug.

B2. Folic acid: Grade of evidence: A
Typical dose: 5 mg once weekly, preferably the day after the methotrexate [9]. Folic acid can be given any day as long as it is not on the same day as methotrexate. Folic acid reduces toxic effects and improves continuation of therapy and compliance [9–11].

C. Route of administration
Methotrexate: Oral, i.m., i.v. or subcutaneous
Oral (licensed): It is preferable to use only 2.5 mg tablets and patients should be reminded of the need to check the dose and strength of the tablets with each prescription.
Parenteral (licensed): The dose for parenteral use is usually the same as the oral although one should consider the difference in bioavailibility between oral and parenteral routes of administration. [12].
Folic Acid: Oral.

D. Time to response: 6 weeks to 3 months

E. Cautions: Grade of evidence: C

(1) Patients with clinically significant renal impairment from any cause (see section J).
(2) Localized or systemic infection including hepatitis B or C and history of tuberculosis.
(3) Unexplained anaemia and/or cytopenia associated with marrow failure.

F. Contraindications: Grade of evidence: C

(1) Pregnancy and breast feeding.
(2) Suspected local or systemic infection.
(3) Bone marrow failure with unexplained anaemia and cytopenia.

G. Notable drug interaction (refer to BNF and SPC)

(1) Phenytoin: Antifolate effect of methotrexate is increased.
(2) Probenecid, penicillin, NSAIDs: Methotrexate excretion is reduced. (Clinically significant interaction between NSAID and methotrexate is rare).
(3) Tolbutamide: Serum concentration of methotrexate may be increased.
(4) Co-trimoxazole, trimethoprim: Antifolate effect of methotrexate is increased and greatly increases the risk of marrow aplasia.

H. Monitoring schedule: Grade of evidence: C [2]

	BSR	BAD
(a) Pre-treatment assessment	FBC, U&E, LFT and CXR (unless CXR done within the last 6 months). Pulmonary function tests should be considered in selected patients [See section H(4)].	
(b) Monitoring	FBC, U&E, LFT every 2 weeks until dose of methotrexate and monitoring stable for 6 weeks; thereafter monthly [9] until the dose and disease is stable for 1 yr. Thereafter the monitoring may be reduced in frequency, based on clinical judgement with due consideration for risk factors including age, comorbidity, renal impairment, etc when monthly monitoring is to continue. Re: Serum pro-collagen III in patients with psoriatic arthritis—refer section J.	Initially once a week FBC, U&E, creatinine, LFTs; gradually increase interval between tests until therapy stabilized; thereafter monitor every 2–3 months.

CXR: chest X-ray.

I. Actions to be taken: Grade of evidence: C [13]

WBC $<3.5 \times 10^9$/l	Withhold until discussed with specialist team.
Neutrophils $<2.0 \times 10^9$/l	Withhold until discussed with specialist team.
Platelets $<150 \times 10^9$/l	Withhold until discussed with specialist team.
AST, ALT > twice upper limit of reference range	Withhold until discussed with specialist team.
Albumin-unexplained fall (in absence of active disease)	Withhold until discussed with specialist team.
Rash or oral ulceration, nausea and vomiting, diarrhoea	Withhold until discussed with specialist team.
New or increasing dyspnoea or dry cough	Withhold and discuss urgently with specialist team.
MCV >105 fl	Withhold and check serum B12, Folate and TFT and discuss with specialist team if necessary.
Mild to moderate renal impairment	Withhold until discussed with specialist team (refer BNF).
Severe sore throat, abnormal bruising	Immediate FBC and withhold until the result of FBC is available.

J. Special clinical circumstances:

Alcohol	C	Cautions required and advise to stay well within national recommendations.	Caution required and advise to stay within 4–6 units/ week [14].
Liver biopsy	B	Liver biopsy is not required in absence of pre-existing liver disease. CSLD is uncommon/rare [15, 16].	Not recommended as a routine but patients with persistently abnormal pro-collagen III (>4.2 μg/l, in at least three samples over a 12 month period) should be considered [17].
Serum pro-collagen III	B	Role of this test in the background of inflammatory arthritis remains unclear–not routinely recommended [18].	Recommended for early detection of liver disease [17, 19].
PFT	B	Methotrexate is best avoided in established cases of ILD. If pre-treatment CXR is abnormal consider HRCT and PFT [20–27]. TLCO can be more sensitive than CXR in some cases [28].	Lung injury in psoriasis or following treatment with methotrexate is rare. If suspected the BSR regimen may be followed.
Bone marrow failure (anaemia, neutropenia and thrombocytopenia)	C	Withdraw methotrexate; if severe, discuss with haematologist, may need immediate admission for urgent folinic acid rescue. (Section M1) [13].	
Renal failure/ severe dehydration	C	Patients who develop dehydration, pre-renal or acute renal failure while on methotrexate should have methotrexate withheld and should be given folinic acid rescue [29] (Section M1). Methotrexate elimination is predominantly by renal excretion. If patients develop worsening chronic renal failure FBC should be monitored closely and dose reduction considered.	
Pregnancy and breast feeding	C	Avoid conception and pregnancy, male and female. To continue contraception for at least 3 months after stopping methotrexate [2, 30, 31].	
Elective surgery	A	Therapy can be continued. Caution for early detection of infection and complications [32, 33].	
NSAIDs	C	Most NSAIDs can be continued as long as monitoring is regular and caution is exercised regarding LFT and renal function, particularly in the elderly [13].	

TABLE 1. Summary

Special circumstances	Grade of evidence	BSR	BAD
Alcohol	C	Cautions required and advise to stay well within national recommendations.	Caution required and advise to stay within 4–6 units/ week [14].
Liver biopsy	B	Liver biopsy is not required in absence of pre-existing liver disease. CSLD is uncommon/rare [15, 16].	Not recommended as a routine but patients with persistently abnormal pro-collagen III (>4.2 μg/l, in at least three samples over a 12 month period) should be considered [17].
Serum pro-collagen III	B	Role of this test in the background of inflammatory arthritis remains unclear–not routinely recommended [18].	Recommended for early detection of liver disease [17, 19].
PFT	B	Methotrexate is best avoided in established cases of ILD. If pre-treatment CXR is abnormal consider HRCT and PFT [20–27]. TLCO can be more sensitive than CXR in some cases [28].	Lung injury in psoriasis or following treatment with methotrexate is rare. If suspected the BSR regimen may be followed.
Bone marrow failure (anaemia, neutropenia and thrombocytopenia)	C	Withdraw methotrexate; if severe, discuss with haematologist, may need immediate admission for urgent folinic acid rescue. (Section M1) [13].	
Renal failure/ severe dehydration	C	Patients who develop dehydration, pre-renal or acute renal failure while on methotrexate should have methotrexate withheld and should be given folinic acid rescue [29] (Section M1). Methotrexate elimination is predominantly by renal excretion. If patients develop worsening chronic renal failure FBC should be monitored closely and dose reduction considered.	
Pregnancy and breast feeding	C	Avoid conception and pregnancy, male and female. To continue contraception for at least 3 months after stopping methotrexate [2, 30, 31].	
Elective surgery	A	Therapy can be continued. Caution for early detection of infection and complications [32, 33].	
NSAIDs	C	Most NSAIDs can be continued as long as monitoring is regular and caution is exercised regarding LFT and renal function, particularly in the elderly [13].	

(1) Alcohol: Any patient suspected of alcohol abuse is usually unsuitable for methotrexate therapy. Dermatologists (BAD) may allow patients, receiving methotrexate, to continue taking small amounts of alcohol (4–6 units/week) [17]. Rheumatologists should advise the patients receiving methotrexate to limit their alcohol intake well within national recommendations.

(2) Hepatotoxicity: Methotrexate related hepatotoxicity was first reported in psoriasis patients several decades ago. A cumulative dose of 1.5 g of methotrexate might cause clinically significant liver disease [34]. Please note that liver fibrosis/cirrhosis may occur with normal liver enzymes and imaging findings [34, 35].

(a) Liver biopsy: Grade of evidence: B
Current studies in patients with RA suggest that liver biopsies are not cost effective for at least the first 10 yrs of methotrexate use in patients with normal liver function values [8]. Clinically serious liver disease (CSLD) is rarely seen in RA patients receiving low dose methotrexate and routine liver biopsies are therefore not recommended [16].

BAD does not recommend routine liver biopsy on all patients receiving methotrexate. However, if there is history of pre-existing liver disease, a baseline ultrasound guided liver biopsy should be performed. This should be undertaken soon after the methotrexate is started, usually within 3–4 months [34, 35].

(b) Serum pro-collagen III levels: Grade of evidence: B
Dermatologists (BAD) have recently examined the role of serological markers such as pro-collagen III amino terminal peptide (PIIINP) in detecting methotrexate-induced liver damage. A recent study suggests that the patients with repeated normal levels of PIIINP are very unlikely to have significant liver damage from fibrosis/cirrhosis [17] and that follow-up liver biopsies may only be offered to patients with persistently abnormal levels of PIIINP over 4.2 ng/ml (for Orion assay)—section M2.

In rheumatology, the role of such serological markers is unclear as it can be false positive in inflammatory arthritis, such as rheumatoid or psoriatic arthritis [18].

(3) Pulmonary toxicity: Pulmonary toxicity related to methotrexate is often the cause for withdrawal of therapy in an otherwise stable patient with a frequency of 1:108 patient years compared with 1: 35 patient years for hepatotoxicity [21] and 1: 58 patient years for neutropenia [36]. Methotrexate pneumonitis (MP) is a potentially fatal hypersensitivity reaction and is far less predictable than hepatic or haematological toxicity. It is most frequently but not exclusively seen within the first year of treatment [28]. Many studies suggest that the incidence of MP is much higher in patients with pre-existing lung disease [20–27].

(4) Pulmonary Function Test (PFT): Grade of evidence: B
PFT may be a useful investigation to detect pre-existing lung disease and is a sensitive but non-specific test in identifying occult lung disease. If pre-treatment CXR suggests abnormal shadowing it may be worth considering a high resolution computerized scan (HRCT) and PFT to ascertain the carbon monoxide transfer factor (TLCO) prior to commencing methotrexate therapy [26]. One recent study suggests carbon monoxide transfer factor (TLCO) is a more sensitive marker for detection of Interstitial Lung Disease (ILD) than CXR [36, 37]. In fact the study proposes the use of PFT as a screening test and recommends that patients with a TLCO value <70% should be subjected to a HRCT (and CXR) [27]. It is important to note that airway obstruction may not be a contraindication to the use of methotrexate but presence of interstitial lung disease certainly is, and it is better detected prior to commencement of therapy or avoided (Dr Clive Kelly, Gateshead Hospital, personal communication).

(5) Bone marrow failure: Grade of evidence: C
Significant fall in cell counts can occur as a result of methotrexate-induced bone marrow suppression. It is particularly likely in the elderly and in patients with significant renal impairment or in patients with concomitant administration of anti-folate drugs. If there is a significant fall in cell count, the following actions should be taken immediately:

(a) Withdraw the methotrexate therapy.
(b) Give folinic acid rescue therapy: Section M1.
(c) Consider immediate discussion with supervising specialist/team, medical on-call team or the local haematologist.

However, in cytopenia due to Felty's syndrome—methotrexate might be a useful drug with good haematological outcome [6].

(6) Pregnancy and breast feeding: Grade of evidence: C
All patients, male and female, should be advised against conception and pregnancy during treatment with methotrexate as it is an abortificient as well as a teratogenic drug. If patients become pregnant inadvertently, it is appropriate to refer the patient to an obstetrician. Breast feeding should not be allowed as the drug may be excreted in the breast milk. Patients should be advised to continue contraception for at least 3 months after stopping methotrexate [30, 31].

(7) Surgical interventions: Grade of evidence: A
Earlier studies suggested an increased incidence of early post-operative complications, such as infections, in a significant number of patients who continued their treatment with methotrexate within 4 weeks of surgery. Two recent studies, one prospective randomized controlled, suggest that the continuation of methotrexate treatment does not increase the risk of infection or surgical complications in patients with RA [32, 33].

(8) NSAIDs: Grade of evidence: C
NSAIDs can be continued as long as monitoring is regularly undertaken. Special cautions need to be exercised if significant abnormalities are noted in liver enzymes. All patients should be regularly advised to avoid over the counter medications including aspirin and ibuprofen [2] without the knowledge of the specialist team.

(9) Infections: Grade of evidence: B
In contrast to many immunosuppressive therapies, methotrexate is relatively safe and has a low risk of infection associated with its use [38]. However, infections are still reported and such infections need to be diagnosed at an early stage to prevent systemic dissemination, and methotrexate should be stopped immediately. If infection is associated with dehydration and pre-renal failure, stop methotrexate and consider folinic acid rescue. The infections can be due to a range of organisms, from viral and bacterial to rare opportunistic infections. One recent short-term observational study (over 6 months) showed a high death rate (33%) in patients with pulmonary infections [39]. Significant mortality and morbidity can be associated with viral infections due to Herpes Zoster/Varicella.

K. Immunization

(1) Patients receiving methotrexate must not receive immunization with live vaccines. Inactivated polio is available although suboptimal response may be seen.
(2) Annual flu vaccination is recommended.
(3) In patients receiving methotrexate exposed to chickenpox or shingles, passive immunization should be carried out using VZIG. The Herpes Zoster immunoglobulins can be obtained from Health Protection Agency. Tel. No: 020 8200 6868.

L. Unresolved and evolving issues

Issues that may be considered for future research/audit are as follows:

(1) Role of serological testing for Hepatitis and Varicella prior to starting methotrexate.
(2) Role of testing serum/red cell folate prior to commencing methotrexate.
(3) Role of pro-collagen III in assessment of liver fibrosis in RA.

M. Appendices

(1) Folinic acid rescue: Grade of evidence: C [2, 40].
In suspected cases of methotrexate overdose, severe haematological toxicity, pre-renal or acute renal failure, consider treatment with folinic acid. The initial dose should be at least 20 mg, given intravenously. Subsequent doses of 15 mg (which may be taken orally) should be given at 6 hourly intervals until the haematological abnormalities are improved (usually not more than 2–8 doses).

(2) Psoriasis treatment (BAD)—PIIINP, Manchester protocol: Grade of evidence: C
Where possible, serum should be collected for PIIINP measurement prior to starting methotrexate. It should subsequently be measured every 2–3 months during continued treatment.

(a) Indications for considering liver biopsy:

(i) Elevation of pre-treatment PIIINP above 8.0 μg/l
(ii) Elevation of PIIINP above normal range (1.7–4.2 μg/l) in at least three samples over a 12 month period.
(iii) Elevation of amino terminal peptide of Type III procollagen (PIIINP) above 8.0 μg/l in two consecutive samples.

(b) Indications for considering withdrawal of methotrexate:

(i) Elevation of PIIINP above 10 μg/l in at least three samples in one 12 month period.

The decision whether to perform liver biopsy, withdraw or continue treatment despite raised PIIINP levels must also take into account other factors, such as disease severity, patient age and the ease with which alternative therapies may be used in place of methotrexate.

References

Methotrexate

1 Kremer JM. Historical overview of the treatment of Rheumatoid arthritis with an emphasis on methotrexate. J Rheumatol 1996;23(Suppl 44):34–7.
2 British National Formulary 48. Pharmaceutical Press, 2004.
3 Saporito FC, Menter MA. Methotrexate and psoriasis in the era of new biologic agents. J Am Acad Dermatol 2004;50:301–9.
4 Feagan BG, Rochon J, Fedorak RN *et al.* Methotrexate for the treatment of Crohn's disease. N Engl J Med 1995;332:292–7.
5 Williams HC, Pembroke AC. Methotrexate in the treatment of vasculitic cutaneous ulcerations in rheumatoid arthritis. J R Soc Med 1989;82:763.
6 Wassenberg S, Herborn G, Rau R. Methotrexate treatment in Felty's syndrome. Br J Rheumatol 1998;37:908–11.
7 American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. Arthritis Rheum 1996;39:723–31.
8 Jones KW, Patel S. A family physician's guide to monitoring methotrexate. Am Fam Physician 2000;62:1607–12.
9 Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. Rheumatology 2004;43;267–71.
10 Ortiz Z, Shea B, Suarez-Almazor ME, Moher D, Wells GA, Tugwell P. The efficacy of folic acid and folinic acid in reducing methotrexate gastrointestinal toxicity in rheumatoid arthritis. A metaanalysis of randomised controlled trials. J Rheumatol 1998;25:36–43.
11 Morgan SL, Baggott JE, Vaughn WH *et al.* Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis: a double-blind placebo-controlled trial. Ann Intern Med 1994;121:833–41.
12 Jundt JW, Browne BA, Fiocco GP, Steele AD, Mock D. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. J Rheumatol 1993;20:1845–9.
13 British Society for Rheumatology. National guidelines for the monitoring of second line drugs, 2000. www.rheumatology.org.uk/
14 West SG. Methotrexate hepatotoxicity. Rheum Dis Clin North Am 1997;23:883–915.
15 Kremer JM. Liver biopsies in patients with rheumatoid arthritis receiving methotrexate: where are we going? J Rheumatol 1992;19:189–91.
16 Kremer JM, Alarcón GS, Lightfoot R Jr *et al.* Methotrexate for rheumatoid arthritis. Suggested guideline for monitoring liver toxicity. American College of Rheumatology. Arthritis Rheum 1994;37:316–28.
17 Chalmers RJG, Kirby B, Smith A *et al.* Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring patients with psoriasis receiving long-term methotrexate: a multicentre audit and health economic analysis. Br J Dermatol 2005;152:444–50.
18 Zachariae H, Aslam HM, Bjerring P, Søgaard H, Zachariae E, Heickendorff L. Serum aminoterminal propeptide of type III procollagen in psoriasis and psoriatic arthritis: relation to liver fibrosis and arthritis. J Am Acad Dermatol 1991;25:50–3.
19 Boffa MJ, Smith A, Chalmers RJ *et al.* Serum type III procollagen aminopeptide for assessing liver damage in methotrexate-treated psoriatic patients. Br J Dermatol 1996;135:538–44.
20 Schnabel A, Richter C, Bauerfeind S, Gross WL. Bronchoalveolar lavage cell profile in methotrexate induced pneumonitis. Thorax 1997;52:377–9.
21 Fuhrman C, Parrot A, Wislez M *et al.* Spectrum of CD4 to CD8 T-cell ratios in lymphocytic alveolitis associated with methotrexate-induced pneumonitis. Am J Respir Crit Care Med 2001;164:1186–91.
22 Akoun GM, Mayaud CM, Touboul JL, Denis M. Methotrexate-induced pneumonitis: diagnostic value of bronchoalveolar lavage cell data. Arch Intern Med 1986;146:804–5.
23 Searles G, McKendry RJ. Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors. Four case reports and review of the literature. J Rheumatol 1987;14:1164–71.
24 Padley SP, Adler B, Hansell DM, Müller NL. High-resolution computed tomography of drug-induced lung disease. Clin Radiol 1992;46:232–6.
25 Suwa A, Hirakata M, Satoh S, Mimori T, Utsumi K, Inada S. Rheumatoid arthritis associated with methotrexate-induced pneumonitis: improvement with i.v. cyclophosphamide therapy. Clin Exp Rheumatol 1999;17:355–8.
26 Alarcón GS, Kremer JM, Macalusco M *et al.* Risk factors of methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicentre, case-control study. Methotrexate-Lung Study Group. Ann Intern Med 1997;127:356–64.
27 Saravanan V, Kelly CA. Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis. Rheumatology 2004;43:143–7.
28 Imokawa S, Colby TV, Leslie KO, Helmers RA. Methotrexate Pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J 2000;15:373–81.
29 Strang A, Pullar T. Methotrexate toxicity induced by acute renal failure. J R Soc Med 2004;97:536–7.
30 Donnenfeld AE, Pastuszak A, Noah JS, Schick B, Rose NC, Koren G. Methotrexate exposure prior to and during pregnancy. Teratology 1994;49:79–81.
31 Chakravarty EF, Sanchez-Yamamoto D, Bush TM. The use of disease modifying antirheumatic drugs in women with rheumatoid arthritis of childbearing age: a survey of practice patterns and pregnancy outcomes. J Rheumatol 2003;30:241–6.
32 Bridges SL Jr, López-Méndez A, Han KH, Tracy IC, Alarcón GS. Should methotrexate be discontinued before elective orthopedic surgery in patients with rheumatoid arthritis? J Rheumatol 1991;18:984–8.
33 Grennan DM, Gray J, Loudon J, Fear S. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Ann Rheum Dis 2001;60;214–7.
34 Roenigk HH Jr, Auerbach R, Maibach H, Weinstein G, Lebwohl M. Methotrexate in psoriasis: Consensus Conference. J Am Acad Dermatol 1998;38:478–85.
35 Kuijpers AL,van de Kerkhof PC. Risk-benefit assessment of methotrexate in the treatment of severe psoriasis. Am J Clin Dermatol 2000;1:27–39.
36 Grove ML, Hassell AB, Hay EM, Shadforth MF. Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. Q J Med 2001;94:309–19.
37 Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography and pulmonary function tests. Thorax 2001;56:622–7.
38 Lovell DJ, Zaoutis TE, Sullivan K. Immunosuppressants, infection and inflammation. Clin Immunol 2004;113:137–9.
39 Abdullah S, Kelly C. Methotrexate related pulmonary complications. ACR Abstract submission, 2004.
40 Chalmers RJG, Boffa MJ. Current management of psoriasis: methotrexate. J Dermatol Treat 1997;8:41–4.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a pro-drug of the active metabolite of mycophenolic acid. It is a suppressor of T and B cell proliferation and adhesion and inhibits inosine monophosphate dehydrogenase that eventually blocks the progression to DNA synthesis and proliferation [1]. It does not inhibit the production of interleukins as does ciclosporin and tacrolimus. MMF has routinely been used in organ transplantation for many years and this remains the licensed indication for its use.

A. Indications: (Unlicensed) RA [2], systemic lupus erythematosus and lupus nephritis [3] and inflammatory myopathy such as dermatomyositis and polymyositis [4, 5]. It has also been used in psoriasis [6], atopic dermatitis and autoimmune bullous dermatoses such as pemphigus. It is also being used in randomized clinical trials in scleroderma, vasculitis and Behçet's disease (Prof. Chris Denton, Royal Free Hospital, London, personal communication).

B. Mycophenolate mofetil dosage: Grade of evidence: C
Typical dose: 1–2 g/day.
Starting dose: 500 mg daily for the 1st week, 500 mg twice daily for the 2nd week and increase it gradually by 500 mg

each week until the optimal or maximum tolerated dose is reached.
Maximum dose: Up to 3 g/day [2].

C. Route of administration:
Oral tablets (250 mg capsules) and suspension.
i.v. infusion–available (see BNF).

D. Time to response: 6 weeks to 3 months

E. Cautions: Grade of evidence: C

(1) Patients with suspected lymphoproliferative disorder or unexplained anaemia, leucopenia and thrombocytopenia.
(2) Localized or systemic infection.
(3) Very frail and elderly.

F. Contraindications: Grade of evidence: C

(1) Pregnancy and breast feeding.
(2) Localized or systemic infections.

G. Notable drug interactions (refer to BNF and SPC)

(1) Antacids: Containing aluminium and magnesium hydroxide cause a decrease in the absorption of MMF by 33% and bio-availability by 17% [7].
(2) Cholestyramine: May decrease the absorption of MMF and bio-availability by 40% [8].
(3) Probenecid: Prevents renal tubular secretion and causes an increase in plasma concentration of MMF.
(4) Aciclovir: Causes increase in the concentration of both MMF and aciclovir. However, the increase is significant only in renal impairment.

H. Common untoward effects
MMF does not usually cause major organ toxicity [9]. The drug does not cause any mutagenic or chromosome abnormalities [10, 11]. The commonest adverse reactions are as follows:

(1) Gastrointestinal: Diarrhoea, nausea, vomiting, abdominal cramps and dyspepsia.
(2) Uro-genital: Sterile haematuria, urinary tract infection, renal tubular necrosis.
(3) Haematological: Abnormal bruising with or without sore throat may indicate bone marrow failure. Severe neutropenia occurs in 0.5% patients receiving MMF in the full dose. STOP the drug. Check FBC immediately and also discuss with specialist team.
(4) Malignancy: Lymphomas caused by oncogenic viruses and skin tumours.

I. Monitoring schedule: Grade of evidence: C

	BSR	BAD
(a) Pre-treatment assessment	FBC, U&E, LFT's CXR.	Same as BSR.
(b) Monitoring	FBC weekly until dose stable for 4 weeks then fortnightly for 2 months. Monthly, even after patient is stabilized on treatment.	Same as BSR.

J. Actions to be taken: Grade of evidence: C

WBC $<3.5 \times 10^9$/l	Withhold until discussed with the specialist team.
Neutrophils $<2.0 \times 10^9$/l	Withhold until discussed with the specialist team.
Platelets $<150 \times 10^9$/l	Withhold until discussed with the specialist team.
Bruising with or without sore throat	Check FBC immediately and discuss with specialist team.

K. Immunisation

(a) Patients receiving MMF must not receive immunization with live vaccines. Inactivated polio is available although sub-optimal response may be seen.
(b) Annual flu vaccination is recommended.
(c) In patients receiving MMF exposed to chickenpox or shingles, passive immunization should be carried out using VZIG.

L. Caveats:

(1) Infections: It is very important to be observant about any new symptoms of infection as the reported incidence of cytomegalovirus infection is slightly higher [6]. The incidence of infection and sepsis is somewhat similar to that typically observed in the transplant population and it is believed that concentrations of mycophenolic acid do not affect the phagocytosis and killing of the bacteria by the neutrophils [12]. In clinical studies, the incidence of herpes, aspergillus and candida were the same whether mycophenolate or azathioprine was used. Pneumocystis carinii pneumonia was almost non-existent in patients treated with MMF [13].
(2) Leucopenia and neutropenia: It is often difficult to assess the exact cause of leucopenia or neutropenia because many causes may lead to the development of these disorders such as additional immunosuppressive regimens, concomitant medications and viral infections or combination of all the above. It is most commonly seen within the first 6 months. Temporary suspension of MMF for 10–14 days will usually result in recovery of the cell count. Once the cell count recovers, the drug can be re-administered in half the previous dose and gradually increased until a stable dose is attained without any toxic effect [14].
(3) Malignancies: An increased incidence of non-Hodgkin's lymphoma has been documented in transplant patients receiving MMF. The majority of malignancies are B cell lymphoma associated with Epstein-Barr virus [15]. However, concomitant treatment with drugs such as azathioprine, ciclosporin or tacrolimus can increase the probability of lymphoma [15].
(4) Pregnancy and breast feeding: It is generally advised to ensure that the patients are NOT pregnant before the drug is commenced and advised to use contraception for at least 6 weeks after discontinuation of treatment [8]. It is not recommended for mothers who are breast feeding (manufacturer's advice).

References

Mycophenolate mofetil

1 Taylor DO, Ensley RD, Olsen SL, Dunn D, Renlund DG. Mycophenolate mofetil (RS-61443): preclinical, clinical and three-year experience in heart transplantation. J Heart Lung Transplant 1994;13:571–82.
2 Goldblum R. Therapy of rheumatoid arthritis with mycophenolate mofetil. Clin Exp Rheumatol 1993;11(Suppl 8):S117–9.
3 Chan TM, Li FK, Tang CSO *et al.* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med 2000;343:1156–62.
4 Tausche AK, Meurer M. Mycophenolate mofetil for dermatomyositis. Dermatology 2001;202:341–3.
5 Majithia V, Harisdangkul V. Mycophenolate mofetil (CellCept): an alternative therapy for autoimmune inflammatory myopathy. Rheumatology 2005;44:386–9.
6 Davison SC, Morris-Jones R, Powles AV, Fry L. Change of treatment from cyclosporin to mycophenolate mofetil in severe psoriasis. Br J Dermatol 2000;143:405–7.
7 Bullingham R, Shah J, Goldblum R, Schiff M. Effects of food and antacid on the pharmacokinetics of single doses of mycophenolate mofetil in rheumatoid arthritis patients Br J Clin Pharmacol 1996;41:513–6.
8 CellCept (mycophenolate mofetil capsules) Product information package insert (June 1995). New Jersey, USA: Roche Laboratories Inc., 1995.
9 The International MMF Renal Transplant Study Group. A pooled analysis of three randomized double-blind clinical studies in prevention of rejection with mycophenolate mofetil in renal allograft recipients (the 1-year analysis). American Society of Transplant Physicians 15th Annual Meeting 1996. www.a-s-t.org/

10 The Mycophenolate Mofetil Renal Refractory Rejection Study Group. Mycophenolate mofetil for the treatment of refractory, acute, cellular renal transplant rejection. Transplantation 1996;61:722–9.
11 Sollinger HW, Belzer FO, Deierhoi MH *et al.* RS-61443 (mycophenolate mofetil). A multicenter study for refractory kidney transplant rejection. Ann Surg 1992;216;513–9.
12 Young CJ, Sollinger HW. Mycophenolate mofetil (RS- 61443). In Kupiec-Weglinski JW, ed. New immunosuppressive modalities in organ transplantation. Austin. Texas: RG Landes Company, 1994;1:17.
13 Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. Transplantation 1995;60:225–32.
14 Giblett ER, Anderson JE, Cohen F, Pollara B, Meuwissen HJ. Adenosine-deaminase deficiency in two patients with severely impaired cellular immunity. Lancet 1972;2:1067–9.
15 Eugui EM, Allison AC. Immunosuppressive activity of mycophenolate mofetil. Ann N Y Acad Sci 1993;685:309–29.

Sodium aurothiomalate

A. Indications: (Licensed) RA, juvenile idiopathic arthritis. (Unlicensed) skin diseases including pemphigus.

B. Dose: Grade of evidence: C
Typical dose: 10 mg test dose (which should be given in the clinic followed by 30 min observation to look for signs of allergic reaction) followed by 50 mg weekly until there is a significant response [1, 2] or a total dose of 1000 mg has been given. In patients who respond, the interval between doses may be increased by stages from 50 mg per week to 50 mg every 4 weeks [3].

C. Route of administration: deep i.m. injection

D. Time to response: Benefit should not to be expected until a cumulative dose of at least 500 mg has been given. If there is no response after a cumulative dose of 1000 mg has been given, consider alternative DMARD therapy [3].

E. Caution: Grade of evidence: C
Elderly, renal or hepatic impairment (moderate); history of urticaria, eczema or inflammatory bowel disease [3].
Anaphylactoid or nitritoid reactions are rare but may occur just a few minutes after the injection. Dizziness, nausea, vomiting, sweating, and facial flushing characterize them. Sodium aurothiomalate treatment should be discontinued [4].

F. Contraindications: Grade of evidence: C

(1) Severe renal or hepatic impairment.
(2) History of blood disorders or marrow aplasia.
(3) Exfoliative dermatitis.
(4) Systemic lupus erythematosus.
(5) Necrotising enterocolitis.
(6) Significant pulmonary fibrosis.
(7) Porphyria.
(8) Pregnancy and lactation: Avoid in pregnancy and during breast feeding [3, 4].
(9) Live vaccines are not recommended in patients receiving sodium aurothiomalate.

G. Monitoring schedule: Grade of evidence: C

	BSR
(a) Pre-treatment assessment [1, 2, 5]	FBC, urinary dipstick for protein, U&E, creatinine, LFTs.
(b) Monitoring [1, 2, 5, 6]	FBC and urinalysis at the time of each injection. The patient should be asked about presence of rash or mouth ulcers before each injection.

Provided blood results are stable, the results of the FBC need not be available before the injection is given but must be available before the next injection, i.e. it is permissible to work one FBC in arrears. Urinalysis should be carried out just before each injection [6].

H. Actions to be taken. Grade of evidence: C

WBC $<3.5 \times 10^9$/l [1, 2, 5]	Withhold until discussed with specialist team.
Neutropaenia $<2.0 \times 10^9$/l [1, 2, 5]	Withhold until discussed with specialist team.
Eosinophilia $> 0.5 \times 10^9$/l	Caution and increase vigilance required.
Platelets $<150 \times 10^9$/l [1, 2, 5]	Withhold until discussed with specialist team.
2+ proteinuria or more [1, 2, 5]	Check MSSU: If infection present treat appropriately. If sterile and 2+ proteinuria or more persists, withhold until discussed with specialist team.
Rash (usually itchy) or oral ulceration [1, 2, 5, 7]	Withhold until discussed with specialist team.
Abnormal bruising or severe sore throat [1, 2, 5, 7]	Check FBC immediately and withhold until results are available.

References

Sodium aurothiomalate

1 British Society for Rheumatology. National guidelines for the monitoring of second line drugs, 2000. www.rheumatology.org.uk
2 White CE, Cooper RG. Prescribing and monitoring of disease-modifying anti-rheumatic drugs (DMARDs) for inflammatory arthritis. In: collected reports on the rheumatic diseases, 2005. Arthritis Research Campaign. Available at: http://www.arc.org.uk/arthinfo/documents/6508.pdf
3 British National Formulary 48. Pharmaceutical Press, 2004.
4 Summary of product characteristics myocrisin. UK: JHC Healthcare Ltd, 2004.
5 Interface Pharmacist network specialist medicines, Rheumatology Shared care guidelines, Sodium aurothiomalate injection October 2006. Available at: www.ipnsm.n-i.nhs.uk/library/SODIUMAUROTHIOMALATESCGOCT06.pdf, (10 March 2008, date last accessed).
6 American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum 2002;46:328–46.
7 Clark P, Tugwell P, Bennet K *et al.* Injectable gold for treating rheumatoid arthritis. Cochrane Database Syst Rev 2000;2:CD000520.

Sulfasalazine

A. Indications: (Licensed) RA, ulcerative colitis and Crohn's disease. (Unlicensed) Sero-negative spondyloarthropathy including psoriatic arthritis and psoriasis.

B. Sulfasalazine dosage: Grade of evidence: C
Typical dose: 500 mg/day increasing by 500 mg weekly to 2.0–3.0 g/day. Occasionally doses above 3.0 g/day are prescribed [1].

C. Route of administration: Oral

D. Time to response: Minimum of 3 months

E. Caution: Grade of evidence: C and B

(1) Glucose-6-phosphate dehydrogenase deficiency: May cause haemolysis [1–3].
(2) Renal impairment (moderate): May cause significant crystalluria and must ensure high fluid intake. In case of severe renal failure: Avoid.
(3) Slow–acetylators of the drug: May cause drug-induced lupus-like syndrome [2, 3]. It is not necessary to assess acetylator phenotype.
(4) May impair folate absorption [1].
(5) Pregnancy and breast feeding [1, 2].
(6) Sulfasalazine can be prescribed to men of childbearing potential although there may be transient reversible oligospermia [4, 5].
(7) If sulfasalazine is to be prescribed during pregnancy, an analysis of risks and benefits to the mother should be undertaken, against the possible small risk related to the unborn child and doses should not exceed 2 g/day [4, 5].
(8) Folic acid: a supplement should be prescribed to those trying to conceive and during pregnancy [6, 7].
(9) Small amounts of the drug may be excreted in breast milk although these are not thought to be a risk to a healthy infant [8].

F. Contraindications: Grade of evidence: C and B
Hypersensitivity to sulphonamides/co-trimoxazole [1, 2] or aspirin [2].

G. Notable drug interactions (refer to BNF and SPC)

(1) Azathioprine may contribute to bone marrow toxicity.
(2) Cardiac glycosides—possibly reduces absorption of digoxin [1, 2].

H. Monitoring schedule: Grade of evidence: C

	BSR and BAD
(a) Pre-treatment assessment	FBC, U&E's creatinine, LFTs.
(b) Monitoring	FBC and LFTs (including AST/ALT) monthly for the first 3 months and 3 monthly thereafter. If, following the first year, dose and blood results have been stable, frequency of blood tests can be reduced to every 6 months for the second year of treatment. Thereafter, monitoring of blood for toxicity may be discarded. Patient should be asked about the presence of rash or oral ulceration at each visit.
(c) Following dose changes	Repeat FBC, LFT one month after dose increases.

I. Actions to be taken: Grade of evidence: C

WBC $<3.5 \times 10^9$/l	Withhold until discussed with specialist team.
Neutrophils $<2.0 \times 10^9$/l	Withhold until discussed with specialist team.
Platelets $<150 \times 10^9$/l	Withhold until discussed with specialist team.
AST, ALT > twice upper limit of reference range	Withhold until discussed with specialist team.
MCV > 105 fl	Check B12, folate and TSH. If abnormal, treat any underlying abnormality. If normal, discuss with the specialist team.
Nausea/dizziness/headache	If possible continue, may have to reduce dose or stop if symptoms severe. Discuss with specialist team.
Abnormal bruising or severe sore throat	Check FBC immediately and withhold until results available. Discuss with the specialist team, if necessary.
Unexplained acute widespread rash	Withhold seek urgent specialist (preferably dermatological) advice.
Oral ulceration	Withhold until discussed with specialist team.

J. Unresolved and evolving issues
These issues may be considered for future prospective clinical audits or research locally, regionally or nationally.

(1) Should folic acid be prescribed for patients receiving sulfasalazine, or should it only be given to patients with pregnancy or malabsorptive disorders of folic acid metabolism?
(2) Should folic acid supplements be given routinely to patients receiving combination therapy with sulfasalazine and azathioprine in RA?

References

Sulfasalazine

1 British National Formulary 54. Pharmaceutical Press, 2007.
2 Salazopyrin summary of Product characteristics http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentID=3344 (18 October 2007, date last accessed).
3 Sweetman S. Martindale: the complete drug reference. Pharmaceutical Press, 2002.
4 Nørgård B, Czeizel AE, Rockenbauer M, Olsen J, Sørensen HT. Population-based case control study of the safety of sulfasalazine use during pregnancy. Aliment Pharmacol Ther 2001;15:483–6.
5 Ostensen M, Ramsey-Goldman R. Treatment of inflammatory rheumatic disorders in pregnancy: what are the safest treatment options? Drug Saf 1998;19:389–410.
6 Preston S, Needs C. Guidelines on the use of antirheumatic drugs in women during pregnancy and child-bearing age. Ballieres Clin Rheumatol 1990;4:687–98.
7 Hernández-Díaz S, Werler MM, Walker AM, Mitchell AA. Folic Acid antagonists during pregnancy and the risk of birth defects. New Engl J Med 2002;343:1608–14.
8 Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. Arch Intern Med 2000;160:610–9.