



**National Guidelines
For the Monitoring of Second Line Drugs**

Produced by the British Society for Rheumatology

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National Guidelines For the Monitoring of Second Line Drugs

Introduction

This is an updated version of the guidelines first published by the BSR in 1996. They are derived from a number of different sources including current local guidelines, data sheets, published studies (see bibliography) and the views of members. They have been reviewed by a small working group of four rheumatologists (Drs Jane Griffin, Ronald Jubb, Tom Palferman and Tom Pullar). There are no double blind randomised controlled trials comparing different monitoring protocols.

It is anticipated that these guidelines will be adapted for local use. In some places, monitoring is carried out exclusively in the hospital setting. In others, GP's may carry out monitoring using local protocols, with the local rheumatologist providing advice and, where necessary, a backup service. The type of advice offered, especially in relation to 'cut off points', will ultimately depend upon local practice.

These guidelines are not intended to offer an exhaustive list of possible drug adverse effects and interactions and should be used in conjunction with the data sheets.

Although dissemination of this booklet will be via the local rheumatologist, the guidelines are designed to be used by non-rheumatologists, such as practice nurses, general practitioners and nurse specialists (hence the advice – 'discuss with rheumatologist').

Finally, we should like to thank all those who provided copies of local guidelines and commented on the draft versions.

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Chair Working Party on Second Line Guidelines

Andrew Bamji
Chair Clinical Affairs Committee

Auranofin (Ridaura)

A typical dose regimen may be:- 3mg b.d. increasing to 3mg t.i.d. after 4-6 months if necessary.

Pretreatment assessment:- FBC, urinalysis, U&E's, LFT's.

Monitoring:- Monthly FBC and urinalysis. Patient should be asked about the presence of rash or oral ulceration at each visit.

Action to be taken:-

WBC $<4.0 \times 10^9$ /l	withhold <u>until discussed</u> with rheumatologist
Neutrophils $<2.0 \times 10^9$ /l	withhold <u>until discussed</u> with rheumatologist
Platelets $<150 \times 10^9$ /l	withhold <u>until discussed</u> with rheumatologist
>1+ proteinuria on >1 occasion	withhold <u>until discussed</u> with rheumatologist
Rash or oral ulceration	withhold <u>until discussed</u> with rheumatologist
Diarrhoea	increase fibre content of diet or add fibre supplements. May need to reduce dose or if severe stop treatment
Abnormal bruising or sore throat	withhold until FBC result available

Please note that in addition to absolute values for haematological indices a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance.

Azathioprine

A typical dose regimen may be:- 1mg/kg/day increasing after 4 to 6 weeks to 2-3mg/kg/day. Lower doses if there is significant renal or hepatic impairment. If allopurinol is co-prescribed the dose of azathioprine must be cut to 25% of the original dose. Live vaccines should be avoided in patients taking azathioprine.

Pneumovax and annual 'flu vaccine should be given. Passive immunisation should be carried out using Varicella zoster immunoglobulin (VZIG) in non-immune patients if exposed to chickenpox or shingles.

Pretreatment assessment:- FBC, U&E's, creatinine, LFT's.

Monitoring:- FBC weekly for 6 weeks, 2 and 4 weeks after each dose increase and thereafter monthly. LFT's monthly until dose stable.

Action to be taken:-

WBC $<4.0 \times 10^9/l$	withhold <u>until discussed</u> with rheumatologist
Neutrophils $<2.0 \times 10^9/l$	withhold <u>until discussed</u> with rheumatologist
Platelets $<150 \times 10^9/l$	withhold <u>until discussed</u> with rheumatologist
>2 -fold rise in AST, ALT or Alk. Phos (from upper limit of reference range)	withhold <u>until discussed</u> with rheumatologist
Rash or oral ulceration	withhold <u>until discussed</u> with rheumatologist
MCV $>105fl$	investigate and if B12 or folate low start appropriate supplementation
Abnormal bruising or sore throat	withhold until FBC result available

Please note that in addition to absolute values for haematological indices a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance.

Cyclosporin (Neoral)

A typical dose regimen may be:- 2.5mg/kg/day in 2 divided doses increasing after 4 weeks by 25mg increments to a maximum of 4mg/kg/day. Cyclosporin is contraindicated in patients with abnormal renal function or uncontrolled hypertension. There are numerous drug interactions involving cyclosporin and it is recommended that the data sheet is consulted at the time of first prescription and if any other drugs are introduced. In particular, the dose of diclofenac should be halved if cyclosporin is co-prescribed. Colchicine and nifedipine should be avoided. Potassium sparing diuretics should be used with caution. Grapefruit juice should be avoided. Live vaccines should be avoided in patients taking cyclosporin. Experience with cyclosporin in rheumatoid arthritis is relatively short. In addition to potentially serious toxicity there appears to be a large number of troublesome non-serious side-effects too numerous to mention. If in doubt please consult the data sheet. Annual 'flu vaccine should be given.

Pretreatment assessment:-FBC, U&E's (x2), creatinine (x2), LFT's, Lipids. Blood pressure should be normal on 2 separate occasions prior to treatment.

Monitoring:- Serum creatinine and BP fortnightly until the dose has been stable for 3 months and thereafter monthly. FBC, LFTs monthly until dose stable for 3 months and then 3 monthly, serum lipids 6 monthly.

Action to be taken:-

Creatinine rises by 30% of baseline	withhold <u>until discussed</u> with rheumatologist
Abnormal bruising	withhold <u>until discussed</u> with rheumatologist
[Potassium] rises to above normal range	withhold <u>until discussed</u> with rheumatologist
BP rise to abnormal range	discuss with rheumatologist
Significant rise in lipids	withhold <u>until discussed</u> with rheumatologist
Platelets < 150x10 ⁹ /l	withhold <u>until discussed</u> with rheumatologist
>2-fold rise in AST, ALT or Alk. Phos (from upper limit of reference range)	withhold until FBC result available

Leflunomide (Arava)

A typical dose regimen may be:- 100mg daily for three days followed by 20mg daily. This can be reduced to 10mg daily if poorly tolerated. At present it is recommended that Leflunomide should not be used in conjunction with other DMARDs in routine clinical practice. Leflunomide may inhibit the metabolism of warfarin, phenytoin and tolbutamide. It has an extremely long elimination half life and interactions with these drugs and with other DMARDs may occur even after leflunomide has been discontinued. Male and female patients should not procreate within 2 years of discontinuing leflunomide. Blood concentrations of its active metabolite should be measured 2 years after discontinuation before pregnancy occurs.

Leflunomide may cause blood dyscrasias, hepatotoxicity, mouth ulcers, skin rash (including Stevens–Johnson syndrome and toxic epidermal necrolysis), mild increase in blood pressure, GI upset, weight loss, headaches, dizziness, tenosynovitis and hair loss. If a severe undesirable side effect of leflunomide occurs or for any other reason rapid removal of its active metabolite is required a washout procedure with cholestyramine 8G tid or activated charcoal 50G qid, each for 11 days is available. Leflunomide increases susceptibility to infections which should be treated promptly. Live vaccines are contraindicated.

Pretreatment assessment:- FBC, LFTs, U&Es and Blood pressure.

Monitoring:- FBC two weekly for the first six months and then eight weekly. LFTs and blood pressure monthly for the first 6 months and then eight weekly.

Action to be taken:-

WBC < $4 \times 10^9/l$	withhold <u>until discussed</u> with rheumatologist
Neutrophils < $2 \times 10^9/l$	withhold <u>until discussed</u> with rheumatologist
Platelets < $150 \times 10^9/l$	withhold <u>until discussed</u> with rheumatologist
>2-fold rise in ALT or AST (from upper limit of reference range)	withhold <u>until discussed</u> with rheumatologist
Rash, itch or mouth ulcers	withhold <u>until discussed</u> with rheumatologist

Methotrexate

A typical dose regimen may be:- 7.5mg weekly increasing by 2.5mg every 6 weeks to a maximum of 25mg. Lower doses should be used in the frail elderly or if there is significant renal impairment. Regular folic acid supplements are thought to reduce toxicity. Cotrimoxazole or trimethoprim must be avoided in patients taking methotrexate. Excess alcohol should be avoided. Live vaccines should be avoided in patients taking methotrexate. NSAIDs in addition to the above doses of methotrexate are **not** contraindicated. Annual 'flu vaccine should be given.

Pretreatment assessment:- FBC, U&E's, creatinine, LFT's, Chest Xray.

Monitoring:- FBC fortnightly until 6 weeks after last dose increase and provided it is stable monthly thereafter. LFT's (incl. AST or ALT) with each blood test. U&E's 6-12 monthly (more frequently if there is any reason to suspect deteriorating renal function).

Action to be taken:-

WBC $<4.0 \times 10^9/l$	withhold <u>until discussed</u> with rheumatologist
Neutrophils $<2.0 \times 10^9$	withhold <u>until discussed</u> with rheumatologist
Platelets $<150 \times 10^9 /l$	withhold <u>until discussed</u> with rheumatologist
>2 -fold rise in AST, ALT (from upper limit of reference range)	withhold <u>until discussed</u> with rheumatologist
Unexplained fall in albumin	withhold <u>until discussed</u> with rheumatologist
Rash or oral ulceration	withhold <u>until discussed</u> with rheumatologist
New or increasing dyspnoea or cough	withhold <u>until discussed</u> with rheumatologist
MCV $>105fl$	investigate and if B12 or folate low start start appropriate supplementation
Significant deterioration in renal function	reduce dose
Abnormal bruising or sore throat	withhold until FBC result available

Please note that in addition to absolute values for haematological indices a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance.

Penicillamine (Distamine, Pendramine)

A typical dose regimen may be:- 125mg/day increasing by 125mg every 4 weeks to 500mg/day. If no response after a further 3 months increase by 125mg every 4 weeks to 750mg/day. If no response after a further 3 months a further increase by 125mg every 4 weeks to 1g/day may be considered. If no response after 3 months on the maximum dose stop treatment.

Pretreatment assessment:- FBC, urinalysis, U&E's and creatinine.

Monitoring:- *Fortnightly* urinalysis and FBC until on a stable dose and thereafter monthly. Patient should be asked about the presence of rash or oral ulceration at each visit.

Action to be taken:-

WBC<4.0x10 ⁹ /l	withhold <u>until discussed</u> with rheumatologist
Neutrophils<2.0x10 ⁹ /l	withhold <u>until discussed</u> with rheumatologist
Platelets<150x10 ⁹ /l	withhold <u>until discussed</u> with rheumatologist
>1+ proteinuria on >1 occasion	withhold <u>until discussed</u> with rheumatologist
>1+ haematuria on > 1 occasion	withhold <u>until discussed</u> with rheumatologist
Rash or oral ulceration	withhold <u>until discussed</u> with rheumatologist
Alteration of taste	continue treatment (usually settles spontaneously)
Dyspepsia	most likely 2y to NSAID but reduce dose if severe
Abnormal bruising or sore throat	withhold until FBC result available

Please note that in addition to absolute values for haematological indices a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance.

Sodium aurothiomalate (Myocrisin)

A typical dose regimen may be:- 10mg test dose (which should be given in the *clinic* followed by 30 minutes observation) followed by weekly injections of 50mg until significant response. Thereafter either 50mg monthly **or** 50mg fortnightly for three months, 50mg three weekly for three months, and then 50mg monthly. If after a total dose of 1g has been administered no response has occurred treatment should be stopped.

Pretreatment assessment:- FBC, urinalysis, U&E's, serum creatinine, LFTs.

Monitoring:- FBC and urinalysis at the time of each injection. 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. Patient should be asked about the presence of rash or oral ulceration before each injection.

Action to be taken:-

WBC<4.0x10 ⁹ /l	withhold <u>until discussed</u> with rheumatologist
Neutrophils<2.0x10 ⁹ /l	withhold <u>until discussed</u> with rheumatologist
Platelets<150x10 ⁹ /l	withhold <u>until discussed</u> with rheumatologist
>1+ proteinuria on >1 occasion	withhold <u>until discussed</u> with rheumatologist
Rash or oral ulceration	withhold <u>until discussed</u> with rheumatologist
Abnormal bruising or sore throa	withhold until FBC result available

Please note that in addition to absolute values for haematological indices a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance.

Sulphasalazine (Salazopyrine EN)

A typical dose regimen may be:- 500mg/day increasing by 500mg weekly to 2.0-3.0g/day.

Pretreatment Assessment:- FBC, LFT's.

Monitoring:- FBC fortnightly and LFT's (incl. AST or ALT) 4 weekly for the first 12 weeks. FBC and LFT's (including ALT or AST) 12 weekly thereafter. If during the first year of treatment blood results have been stable 6 monthly tests will suffice for the second year and, thereafter, monitoring of blood for toxicity could be discarded. Patient should be asked about the presence of rash or oral ulceration at each visit.

Action to be taken:-

WB $<4.0 \times 10^9$ /l	withhold <u>until discussed</u> with rheumatologist
Neutrophil $<2.0 \times 10^9$ /l	withhold <u>until discussed</u> with rheumatologist
platelets $< 150 \times 10^9$ /l	withhold <u>until discussed</u> with rheumatologist
>2 -fold rise in AST, ALT or Alk. Phos (from upper limit of reference range)	withhold <u>until discussed</u> with rheumatologist
rash or oral ulceration <i>normal</i>	withhold <u>until discussed</u> with rheumatologist
MCV >105 fl	investigate and if B12 or folate low start appropriate supplementation
nausea/dizziness/ headache	if possible continue, may have to reduce dose or stop if symptoms severe.
Abnormal bruising or sore throat	withhold until FBC result available

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