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INTRODUCTION

In inflammatory, and especially rheumatoid, arthritis, the cytokines, proteases and collagenases released from cells in the inflamed synovium can be locally invasive, causing bony destruction at the bone–synovium junction (i.e. erosion formation) and destruction of the articular cartilage within the joint (causing loss of joint space). These features are seen on plain radiographs from as early as 12 months into the disease, but from considerably earlier if magnetic resonance imaging (MRI) is used. The rate at which rheumatoid joint destruction progresses can be assessed radiographically, and a number of elegant prospective studies have clearly shown that the rate of radiographic damage is greatest in the first 3–5 years. It is for this reason that the old hierarchical treatment pyramid for rheumatoid arthritis (RA) (Figure 1) has been abandoned in favour of a more aggressive approach. Disease-modifying anti-rheumatic drugs (DMARDs) are now introduced at a very early stage, namely as soon as the diagnosis is confirmed. The American College of Rheumatology (ACR) diagnostic guidelines for RA dictate that synovitis must have been present for at least 6 weeks before the diagnosis can be confirmed, to avoid self-limiting post-infectious problems (such as parvovirus infections) being labelled as rheumatoid. Once the diagnosis of RA has been made most UK rheumatologists now offer DMARD therapy to affected patients. The same principle applies to the other varieties of inflammatory arthritis problems although, in individual patients, the circumstances may dictate that local therapy is more suitable – for example a B27-related oligoarthritis affecting just one knee may initially be effectively treated by local steroid injections without the need for a DMARD. Overall, however, the number of patients commencing DMARDs is increasing, as more patients with inflammatory arthritis are referred for early diagnosis and treatment.

There is no hard and fast rule about which DMARD to use first in new rheumatoid patients, but sulfasalazine and methotrexate are the usual first choices for most patients in the UK. When these initial choices become unsuitable, through lack of response and/or toxicity,
the next DMARD choice is again arbitrary. It is based on personal experience and preferences, and there is a growing trend to use DMARDs in combination, i.e. to start another DMARD without stopping the currently used one. Thus, patients with ‘drug-resistant’ disease may end up on three or more DMARDs, as well as low-dose prednisolone, within about 2 years of the disease onset. Only time and meticulous trials will tell whether combinations are really better than the single therapy approach.

Some general practitioners (GPs), through their own particular background, may be happy to make decisions regarding DMARD changes, but most will have insufficient expertise to take responsibility for DMARD strategy, which must therefore be provided by the local rheumatologist. DMARDs have a long list of potentially dangerous side-effects, and can only be safely used if carefully monitored. Many GPs play a very important role in ensuring that these drugs are used safely in their patients (through drug monitoring and patient safety surveillance, often in a ‘shared-care’ arrangement). Shared care works well as long as the monitoring instructions are sufficiently clear and everyone (patient, GP and hospital) knows and fulfils their respective roles. Shared-care monitoring is dependent on cooperation, communication and co-ordination of services, and is often supported locally by hospital-based rheumatology nurse specialists, who are usually accessible via telephone help-lines.

Most GPs will only have a small number of patients on DMARDs, and so are unlikely to be familiar with all possible side-effects. To help standardise DMARD monitoring the British Society for Rheumatology (BSR) produced national guidelines to act as a basis for local practice: ‘National guidelines for the monitoring of second line drugs’ (2nd edition, July 2000). These guidelines are felt to represent a safe level of clinical care for patients requiring DMARD treatment, while keeping monitoring time and expenditure down to an acceptable level. This article is based on these guidelines. In the section ‘Prescribing and monitoring information’ in this article, the information shown shaded reproduces the advice given in the BSR guidelines. Non-shaded information is additional to this, provided by the authors. The article thus aims to provide all UK GPs with clear instructions on how to prescribe and monitor the DMARDs in regular use in the UK.

**Provision of patient information regarding DMARDs**

The Arthritis Research Campaign (arc) has produced patient information leaflets for all of the currently used DMARDs. These leaflets are available free to all rheumatology departments and general practices on request (see ‘Further reading’ for details). Some rheumatology departments provide similar locally generated written information. The consultant (or GP where appropriate) should discuss the relevant DMARD with the patient, including information about the therapeutic effects (for example most DMARDs have a slow onset of action, lasting around 3 months), side-effects and monitoring requirements. Where appropriate, a shared-care monitoring booklet should be supplied to the patient in which the hospital- or community-based nurse or doctor should record the monitoring results. This monitoring booklet is designed not as a way of checking up on GP performance, but to provide all involved in that patient’s shared care with an easily interpreted sequential display of the results. This booklet should, where possible, be kept by the patient, who thus becomes his or her own advocate for safety.

**Infections**

Certain DMARDs have clear immunosuppressive properties (e.g. methotrexate, azathioprine), and so can predispose to infections. Patients suffering infections therefore require early assessment and, if necessary, antibiotic treatment. Occasionally infections are severe and may thus require the DMARD to be temporarily stopped. Immunosuppressive regimes also predispose to atypical infections, which should be suspected if ‘simple’ infections do not clear as expected. Prophylaxis with influenza vaccine and pneumovax is recommended. We suggest you refer to the BSR recommendations on vaccinations (see ‘Further reading’).
Pregnancy
As new drugs are becoming available – and information in respect of currently used DMARDs in pregnancy has seen recent changes – it is best to contact your local hospital drug information pharmacist for the most up-to-date information on risks in pregnancy. See also the arc patient information booklet ‘Pregnancy and Arthritis’.

Disease activity monitoring
As most DMARD changes are likely to be made by the attending rheumatologist, s/he will bear the main responsibility for assessing response to treatment, although it is important for GPs to understand the process. A patient’s response to DMARD therapy can be monitored using the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) tests, which both rise in association with an increased acute phase response to inflammation. However, the ESR can be artificially elevated when the inflammatory disease is in fact well controlled, either due to coincidental anaemia (which is common in RA) or with coincidentally elevated circulating levels of immunoglobulins, which coat the red cells and make them ‘sticky’. If the ESR seems inappropriately elevated for the level of disease activity, the CRP or plasma viscosity should also be checked. If the ESR is elevated in association with a normal or near normal CRP, then reduced haemoglobin and/or elevated immunoglobulin levels may be responsible for the elevated ESR in the absence of inflammation.

Duration of treatment
Once the maintenance dose of a DMARD has been reached for the individual patient, that dose will usually continue indefinitely, or until side-effects or lack of efficacy require discontinuation or dosage increase. When drug reactions do occur it is often soon after starting a new drug, hence the extra vigilance and intensity of drug monitoring during the early phase of any new DMARD regime. As the range of DMARDs is relatively small the decision to stop an individual agent should be taken with care, and every effort should be made to maintain patients on such therapies if they are effective. The decision to discontinue a DMARD should usually only be taken after discussion with the local rheumatology department.

Combination therapy
The increasing trend to use DMARD combinations has already been mentioned. Such combinations may not in themselves be more toxic, but each time a new drug is added the monitoring requirements will increase according to the monitoring requirements of the newly started drug. The second or third DMARDs are usually given in their standard doses.

Responsibilities of GPs undertaking monitoring
Irrespective of who has made the recommendation to start/change/add a DMARD, a GP agreeing to monitor the drug should:

- ensure that the necessary blood and urine tests are normal
- ensure that the relevant blood and urine monitoring requirements are undertaken, and at the correct frequency (see below)
- ensure that the blood and urine test results are checked for any abnormality at the same frequency as the tests are being undertaken
- only continue to prescribe a DMARD if it is being satisfactorily monitored
- follow the recommended guideline in the event of a drug reaction or monitoring abnormality
- be alert for any of the known adverse reactions, as outlined for each DMARD below.

The patient also has a responsibility to ensure blood and urine tests are taken at the correct intervals.

MONITORING TOXICITY
Baseline tests are needed to safely preclude certain patients from taking a DMARD which, for them, would represent a specifically high risk. For example, in a patient with coincidental RA and liver disease, methotrexate therapy should clearly be avoided. It is clear from the information given below for each DMARD that certain toxicities are common to a number of the drugs, e.g. marrow toxicity for azathioprine, leflunomide, gold salts, methotrexate and sulfasalazine and renal toxicity for ciclosporin. In general, the monitoring instructions to avoid such toxicities are the same for each drug predisposing to that toxicity, but the interval recommended between each monitoring test varies between the drugs according to their likelihood of causing the toxicity. For instance, intramuscular (IM) gold is more likely than sulfasalazine to cause marrow problems, and so gold requires more intense monitoring than sulfasalazine. Any of the drugs may be the cause of a specific toxicity; GPs may be the first to uncover the problem, and so need to know what to do to minimise any potential dangers resulting from it. Although any of the DMARDs could, through an allergic type reaction, cause any toxic reaction, certain of the drugs are more liable to cause specific toxicities than others, hence the instructions set out below.

Bone marrow toxicity
Azathioprine, leflunomide, gold salts, methotrexate and sulfasalazine can all regularly cause neutropaenia, thrombocytopenia and anaemia, separately or as part of a pancytopenia. In severe cases full-blown aplastic anaemia can occur, especially with gold, and patients may then...
need full marrow support for months or years before marrow recovery occurs. It is thus very important to detect marrow problems early, and especially when they are reversible by DMARD discontinuation. This is the rationale for the monitoring process. Sequentially recording the monitored results will emphasise potentially dangerous trends early. Thus, while a white cell count of <4.0 x 10^9/l may not in itself be dangerous, if it represents part of a steady downward trend then it would be sensible to stop the DMARD and observe. Refer to the guidelines below but, in general, the drug in question should be withheld until the case has been discussed with the relevant rheumatologist when:

- the total white cell count falls to <4.0 x 10^9/l
- the neutrophil count falls <2.0 x 10^9/l
- the platelet count falls to <150 x 10^9/l

These levels are meant to represent a guide, rather than be absolutely directive. Some individuals regularly run platelet counts at or even below 150 x 10^9/l. For them, such a count would not be dangerous, but if the count then fell on therapy this would spell potential danger. GPs have room for sensible discretion, and can safely watch levels near to the lower permitted, and should be watching for further declines very carefully and be willing to withhold treatment if danger seems likely. Most rheumatologists, or their nurse specialists, are keen to discuss any monitoring problem with GPs to reduce the potential dangers of DMARD therapy. If there has been a white cell decline which has gone unnoticed, or has occurred very quickly, patients may present with a flu-like illness, mouth ulcers, or sore throat or with epistaxis, abnormal bruising or bleeding gums.

**Renal toxicity**

Gold and penicillamine can both regularly cause reversible renal damage, ranging from 1+ of proteinuria and/or haematuria to nephrotic syndrome, glomerulonephritis and renal failure. If spotted early on, drug discontinuation will be quickly followed by resolution; again the importance of the monitoring process is emphasised. A trace of proteinuria/haematuria is commonly seen, and can be safely ignored. In general terms, the DMARD should be withheld and the relevant rheumatologist notified if >1+ of proteinuria or haematuria is detected on more than one occasion. If significant proteinuria is detected, a 24-hour urine sample should be arranged to quantify the problem. RA can itself cause renal problems, so protein or blood loss in the urine may signify the onset of a non-drug-related problem which will require investigation. For ciclosporin, renal toxicity is not manifested as haematuria or proteinuria, but as otherwise unexplained elevations of creatinine and blood pressure (BP). Thus, if the plasma creatinine rises by >30 % of its baseline value, or the BP goes into the abnormal range, the drug should be withheld until discussions with the relevant rheumatologist.

**Liver toxicity**

Azathioprine, methotrexate, sulfasalazine and leflunomide can all regularly cause liver problems, which are reversible if the drug is discontinued. In general the DMARD in question should be withheld and the relevant rheumatologist notified if there is a >2-fold increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (Alk Phos) from the upper limit of the local laboratory reference range.

**General toxicity**

*Mucocutaneous:* Any drug may cause any side-effect in any individual, but certain side-effects are more likely. Thus, although any drug may cause a rash, for gold an itchy skin rash is an especially important feature to ask patients about at every monitoring visit. Ignoring a minor gold rash while continuing the therapy risks the development of a generalised rash, or even erythroderma with all its dangers.

**Pulmonary:** Although any drug could theoretically cause an allergically mediated pneumonitis, in practice it is only methotrexate which regularly does so, even if infrequently. Since it may lead on to the development of irreversible lung fibrosis if the drug is not discontinued, it is important to remember that a troublesome dry cough in the early phase of treatment, or on increasing the dose, could be due to a pneumonitis. If there is any possibility of pneumonitis, withhold the drug and discuss with the relevant rheumatologist. Gold can rarely cause irreversible lung fibrosis which is not preceded by symptomatic pneumonitis.

**Gastrointestinal:** While any DMARD could cause nausea and/or vomiting, certain ones are more liable to do so. Sulfasalazine frequently causes mild nausea. This is often accompanied by a headache, and both usually settle after a few days if the drug is continued. If not, that patient is intolerant of the drug. As the dosage is increased for both azathioprine and methotrexate, nausea can be a genuine problem, limiting the tolerability of both drugs. The problem can sometimes be minimised by taking the azathioprine in divided doses, or by giving the methotrexate intramuscularly.

These DMARD monitoring and prescribing guidelines are meant to act as a basis for safe practice. Obviously there may be minor local differences in the practice of individual rheumatologists.

As a general rule, if there is any query regarding the possibility of side-effects, withhold the DMARD and discuss with the rheumatologist overseeing the case.
PREScribing AND MONITORING INFORMATION

Listed below, in alphabetical order, are prescribing and monitoring instructions based on the relevant details of all the DMARDs regularly used to treat rheumatoid and the other inflammatory arthritis conditions in UK rheumatological practice.

Please note: Shading indicates the information given in the BSR guidelines (‘National guidelines for the monitoring of second line drugs’, 2nd edition, July 2000). Other information is additional to this, supplied by the authors.

<table>
<thead>
<tr>
<th>Key to abbreviations</th>
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<td>Alk Phos</td>
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<td>ALT</td>
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<td>AST</td>
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<td>BP</td>
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<td>DMARD</td>
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<td>FBC</td>
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<td>LFTs</td>
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<td>U&amp;Es</td>
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<td>WBC</td>
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AURANOFIN (Ridaura)

Auranofin (oral gold) modifies the immune process – mechanism(s) of action not understood.

Pre-treatment assessment: FBC, urinalysis, U&Es, LFTs.

Administration: Oral, taken with plenty of water with or just after food.

A typical dose regimen may be: 3 mg twice a day increasing to 3 mg three times a day after 4–6 months if necessary.

Time to response: 4–6 months.

Precautions and contraindications: Contraindicated in patients with known renal or hepatic impairment, SLE.

Side-effects:

Haematological: Neutropenia, thrombocytopenia, eosinophilia, and rarely aplastic anaemia

Renal: Proteinuria, which may rarely progress to nephrotic syndrome and haematuria

Mucocutaneous: Rashes and pruritis, sometimes severe, exfoliative dermatitis, photosensitivity

Gastrointestinal: Nausea, reversible taste disturbance (e.g. metallic taste), mouth ulcers, diarrhoea

Other: Rare, but include cholestatic hepatitis, colitis and pulmonary fibrosis

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

Action to be taken:

<table>
<thead>
<tr>
<th>Test</th>
<th>Action</th>
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<tbody>
<tr>
<td>WBC &lt;4.0 x 10^9/l</td>
<td>Withhold until discussed with rheumatologist.</td>
</tr>
<tr>
<td>Neutrophils &lt;2.0 x 10^9/l</td>
<td>Withhold until discussed with rheumatologist.</td>
</tr>
<tr>
<td>Platelets &lt;150 x 10^9/l</td>
<td>Withhold until discussed with rheumatologist.</td>
</tr>
<tr>
<td>&gt;1+ proteinuria on &gt;1 occasion</td>
<td>Withhold until discussed with rheumatologist.</td>
</tr>
<tr>
<td>Rash or oral ulceration</td>
<td>Withhold until discussed with rheumatologist.</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Increase fibre content of diet or add fibre supplements. May need to reduce dose or, if severe, stop treatment.</td>
</tr>
<tr>
<td>Abnormal bruising or sore throat</td>
<td>Withhold until FBC result available.</td>
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</tbody>
</table>

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 (Imuran)**

**Azathioprine** is converted to mercaptopurine, an antimetabolite interfering with nucleic acid synthesis, and so acts as an immunosuppressant agent. Can be used in other autoimmune disorders, e.g. SLE, polymyositis, autoimmune hepatitis.

**Pre-treatment assessment**: FBC, U&Es, creatinine, LFTs.

**Administration**: Oral, swallowed with plenty of water, or just after food to minimise nausea.

**A typical dose regimen may be**: 1 mg/kg/day increasing after 4–6 weeks to 2–3 mg/kg/day.

**Time to response**: Approximately 2–3 months.

**Precautions and contraindications**: Use 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.

**Potential drug interactions**: Caution with rifampicin, warfarin and allopurinol. Reduced response to killed vaccines.

**Side-effects**:
- **Haematological**: Leucopenia, anaemia, neutropenia, thrombocytopenia, macrocytosis, erythroid hypoplasia
- **Hepatic**: Liver dysfunction (tends to be dose-related)
- **Gastrointestinal**: Nausea, loss of appetite, diarrhoea
- **Mucocutaneous**: Urticaria, erythematous pruritus, oral ulceration, alopecia
- **Other**: Myalgia, arthralgia, drug fevers, pancreatitis, opportunistic infections

**Monitoring**: FBC weekly for 6 weeks, 2 and 4 weeks after each dose increase and thereafter monthly. LFTs monthly until dose stable.

**Action to be taken**:
- WBC <4.0 x 10^9/l  Withhold until discussed with rheumatologist.
- Neutrophils <2.0 x 10^9/l  Withhold until discussed with rheumatologist.
- Platelets <150 x 10^9/l  Withhold until discussed with rheumatologist.
- >2-fold rise in AST, ALT or Alk Phos (from upper limit of reference range)  Withhold until discussed with rheumatologist.
- Rash or oral ulceration  Withhold until discussed with rheumatologist.
- MCV >105 fl  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.
**CICLOSPORIN (Neoral)**

**Ciclosporin** is an immunosuppressant agent, originally used to prevent organ graft rejection, which exerts its immunosuppressant action directly through effects on T-lymphocytes. In addition to inflammatory arthritis it is also used in psoriasis, polymyositis etc. This shared-care guideline (SCG) is for rheumatology and dermatology patients only, as a separate SCG exists for transplant patients.

<table>
<thead>
<tr>
<th><strong>Pre-treatment assessment</strong></th>
<th>FBC, U&amp;Es (x 2), creatinine (x 2), LFTs, lipids. Blood pressure should be normal on two separate occasions prior to treatment.</th>
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</thead>
<tbody>
<tr>
<td><strong>Administration</strong></td>
<td>Oral. Patients should avoid taking grapefruit juice or eating grapefruit for 1 hour before and after ingestion. Capsules should be taken 12 hours apart, with plenty of water.</td>
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<tr>
<td><strong>A typical dose regimen may be:</strong></td>
<td>2.5 mg/kg/day in two divided doses increasing after 4 weeks by 25 mg increments to a maximum of 4 mg/kg/day.</td>
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<tr>
<td><strong>Time to response:</strong></td>
<td>Approximately 6 weeks to 3 months.</td>
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<tr>
<td><strong>Precautions and contraindications</strong></td>
<td>Ciclosporin is contraindicated in patients with abnormal renal function or uncontrolled hypertension. There are numerous drug interactions involving ciclosporin 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 ciclosporin 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 ciclosporin. Experience with ciclosporin in RA 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.</td>
</tr>
</tbody>
</table>
| **Side-effects:**          | **Renal**: A frequent and potentially serious complication, dose-dependent. Evident as reversible increase in serum creatinine, and necessitates dose reduction or discontinuation of therapy. Renal damage may follow long-term treatment at toxic doses.  
**Cardiovascular**: Hypertension; may require anti-hypertensive therapy or dose reduction  
**Mucocutaneous**: Hypertrichosis, gingival hypertrophy, rashes  
**Haematological**: Anaemia  
**Gastrointestinal**: Nausea, vomiting, abdominal pain, colitis  
**Hepatic**: Hepatic dysfunction, pancreatitis  
**Nervous system**: Headaches, tremor, neuropathy, confusion, paraesthesiae, convulsions, fatigue  
**Other**: Weight gain, dysmenorrhoea or amenorrhoea, gynaecomastia (particularly when co-administered with spironolactone), hyperkalaemia, hyperuricaemia, hypomagnesaemia, hypercholesterolaemia [?]. A rare syndrome of thrombocytopenia in combination with microangiopathic haemolytic anaemia and renal failure. |
| **Monitoring**             | Serum creatinine and BP fortnightly until the dose has been stable for 3 months and thereafter monthly. FBC, LFTs monthly until dose is stable for 3 months and then 3-monthly, serum lipids 6-monthly. |
| **Action to be taken:**   |  
Creatinine rises by 30% of baseline | Withhold until discussed with rheumatologist.  
[Potassium] rises to above normal range | Withhold until discussed with rheumatologist.  
BP rise to abnormal range | Discuss with rheumatologist.  
Significant rise in lipids | Withhold until discussed with rheumatologist.  
Platelets < 150 x 10⁹/l | Withhold until discussed with rheumatologist.  
>2-fold rise in AST, ALT or Alk Phos (from upper limit of reference range) | Withhold until FBC result available.  
Abnormal bruising | Withhold until discussed with rheumatologist. |

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.
**HYDROXYCHLOROQUINE (Plaquelil)**

**Hydroxychloroquine** is an anti-malarial drug effective in RA and SLE. Mode of action may be related to inhibition of cellular enzyme release and interference with intracellular function.

**Pre-treatment assessment:** Visual acuity assessment, FBC, U&Es, creatinine, LFTs.

**Administration:** Oral; should be taken after food with plenty of water. Some patients find orange juice useful to mask the bitter after-taste.

**A typical dose regimen may be:** 200 mg daily, progressing to a maintenance dose of 200–400 mg daily (aim for 3–5 mg/kg/day).

**Time to response:** Approximately 3–6 months.

**Precautions and contraindications:** Hydroxychloroquine is contraindicated in patients with hepatic and renal impairment or eye conditions. An eye test should be carried out if there is visual disturbance, and for those over 60 years.

**Potential drug interactions:** Antacids decrease absorption, cimetidine increases drug levels. Hydroxychloroquine antagonises anti-epileptics but enhances digoxin.

**Side-effects:**

- **Mucocutaneous:** Pruritic erythematous macular rash occurring soon after treatment commenced. May predispose to photosensitivity – sunscreen advised. Blue-black pigmentation of skin may occur after many years of continuous use.

- **Gastrointestinal:** Nausea, diarrhoea, abdominal cramps.

- **Renal:** Haematuria, proteinuria which may rarely progress to nephrotic syndrome.

- **Ocular:** Cycloplegia, i.e. paralysis of the ciliary muscles manifesting as focusing difficulty and pupillary dilatation (usually of minimal severity), keratopathy (reversible even on continuation of treatment), photophobia (patients should be advised to wear sunglasses in bright light), irreversible retinopathy (maculopathy), but no cases of retinopathy found when treatment for <10 years or when dose <6.5 mg/kg/day [Rheum Dis Clin N Am 1994;20:243-63].

- **Other:** Other rare side-effects include headache, bleaching of skin and hair, proximal myopathy, peripheral neuropathy, thrombocytopenia and agranulocytosis (very rare).

**Monitoring:** Yearly visual acuity assessment unless sudden visual deterioration prompts earlier assessment [Ocular toxicity and hydroxychloroquine: guidelines for screening 2004. Royal College of Ophthalmologists].

**Action to be taken:**

Ophthalmological assessment may be required.
LEFLUNOMIDE (Arava)

Leflunomide is an immunomodulatory agent which arrests activated lymphocytes thought to be involved in inflammatory arthritis pathogenesis. The active metabolite has a half-life of 1–4 weeks, therefore an initial loading dose may be given to reach a therapeutic level in a reasonable time.

Pre-treatment assessment: FBC, LFTs, U&Es, BP.

Administration: Oral, the tablets being swallowed whole with plenty of water. Absorption not affected by food.

A typical dose regimen may be: 100 mg daily for 3 days followed by 20 mg daily. This can be reduced to 10 mg daily if poorly tolerated.

Time to response: Begins after 4–6 weeks, but improvements may continue for 4–6 months.

Precautions and contraindications: 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 BP, gastrointestinal 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 8 g 3 times a day or activated charcoal 50 g 5 times a day, each for 11 days, is available. Leflunomide increases susceptibility to infections, which should be treated promptly. Live vaccines are contraindicated.

Leflunomide is contraindicated in patients with liver impairment or moderate to severe renal failure, serious infections, severe immunodeficiency states (e.g. AIDS), and severe hypoproteinaemia (e.g. nephrotic syndrome).

Potential drug interactions: Other drugs causing liver or marrow toxicity, e.g. methotrexate.

Side-effects:

Mucocutaneous: Eczema, dry skin itching, urticaria, oral ulceration and alopecia (diffuse hair loss may occur in about 10% of patients, usually reversible on dose reduction or discontinuation). NB: In case of ulcerative stomatitis, stop treatment. If Stevens–Johnson syndrome or toxic epidermal necrolysis occur, treatment should be stopped. A complete washout is essential in such cases.

Haematological: Leucopenia, anaemia, mild thrombocytopenia, eosinophilia, and rarely agranulocytosis.

Gastrointestinal: Nausea, vomiting, anorexia, abdominal pain, taste disturbance, diarrhoea (usually self-limiting).

Hepatic: Severe liver dysfunction rare, but small LFT elevations more common. Patients should be advised that alcohol consumption should be avoided, or kept to a minimum.

Nervous system: Headaches, dizziness, asthenia, paraesthesias, anxiety.

Musculoskeletal system: Tenosynovitis, tendon rupture.

Cardiovascular: Hypertension may occur in about 10% of the patients. Pre-existing hypertension predisposes.

Allergic reactions: Mild allergic reactions may occur (rash, pruritus, urticaria). Anaphylaxis rare.

Infection: Severe infection may necessitate stopping drug and administering a washout. Patients with previous tuberculosis need careful monitoring as there is increased risk of reactivation.

Vaccinations: No clinical data is available on the efficacy and safety of vaccinations and leflunomide treatment. Vaccination with live vaccine is thus not recommended. The very prolonged half-life of leflunomide should be considered when contemplating live vaccine after stopping the drug.

Monitoring: FBC fortnightly for the first 6 months and then 8-weekly. LFTs and BP monthly for the first 6 months and then 8-weekly.

Action to be taken:

| WBC <4.0 x 10^9/l | Withhold until discussed with rheumatologist. |
| Neutrophils <2.0 x 10^9/l | Withhold until discussed with rheumatologist. |
| Platelets <150 x 10^9/l | Withhold until discussed with rheumatologist. |
| 2-fold rise in ALT, AST, Alk Phos (from upper limit of reference range) | Withhold until discussed with rheumatologist. |
| Rash, itch or mouth ulcers | Withhold until discussed with rheumatologist. |

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.
METHOTREXATE (Maxtrex)

Methotrexate is a folic acid antagonist and its major site of action is the enzyme dihydrofolate reductase. Its main therapeutic effect is inhibition of DNA synthesis but it also impairs RNA and protein synthesis. It is thus an antimetabolite cytotoxic agent.

Pre-treatment assessment: FBC, U&Es, creatinine, LFTs, chest x-ray.

Administration: Weekly dosage by mouth or by intramuscular injection. To minimise toxicity folic acid is usually co-prescribed. Different rheumatologists have different folic acid regimes and so the folic acid prescriber should be guided by local practice.

A typical dose regimen may be: 7.5 mg weekly increasing by 2.5 mg every 6 weeks to a maximum of 25 mg.

Time to response: 6 weeks to 3 months.

Precautions and contraindications: 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.

Methotrexate is contraindicated in patients with severe anaemia, leucopenia and thrombocytopenia. Methotrexate is teratogenic, so effective contraception is required in treated women of child-bearing age, or treated men whose partner is of child-bearing age, and for 3 months afterwards. Methotrexate may result in a reversible decrease in fertility. As methotrexate is highly protein-bound, and excreted unchanged in urine, it may interact with other drugs. NSAIDs may reduce excretion of methotrexate, so patients on this combination should be monitored carefully. Probenecid can severely inhibit renal excretion of methotrexate, and so is contraindicated.

Potential drug interactions: NSAIDs increase methotrexate toxicity by reducing excretion.

Side-effects:

Haematological: Neutropenia, thrombocytopenia, macrocytosis, and rarely aplastic anaemia.

Hepatic: Cirrhosis and fibrosis – risk factors are alcohol abuse, obesity and previous liver disease. Alcoholism is an absolute contraindication, but 1–2 glasses of wine or 2 pints of beer a week are permitted.

Gastrointestinal: Nausea, vomiting, abdominal pain, diarrhoea.

Pulmonary: An allergically mediated pneumonitis is a rare early complication, manifesting as a troublesome dry cough. If drug not discontinued, pneumonitis may be followed by interstitial fibrosis. The latter may occur without preceding pneumonitis, and can be progressive and thus lethal.

Mucocutaneous: Rashes, urticaria, erythematous pruritus, oral ulceration, skin pain, alopecia.

Renal: Acute tubular necrosis is a rare complication. Renal impairment is a relative contraindication, but therapy may still be used if serum creatinine is monitored and dosage adjusted accordingly.

Other: Headaches, depression, irritability, enteritis. Opportunistic infections may occur. Suppression of ovarian and testicular function may occur.

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

Action to be taken:

- WBC <4.0 x 10^9/l Withhold until discussed with rheumatologist.
- Neutrophils <2 x 10^9/l Withhold until discussed with rheumatologist.
- Platelets <150 x 10^9/l Withhold until discussed with rheumatologist.
- >2-fold rise in AST, ALT, Alk Phos (from upper limit of reference range) Withhold until discussed with rheumatologist.
- Unexplained fall in albumin Withhold until discussed with rheumatologist.
- Rash or oral ulceration Withhold until discussed with rheumatologist.
- New or increasing dyspnoea or cough Withhold until discussed with rheumatologist.
- MCV >105 fl Investigate and if B12 or folate low 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)

**Penicillamine** is indicated in the treatment of several conditions but is used primarily in the treatment of inflammatory arthritis. Its mechanism of action is unknown.

### Pre-treatment assessment

**FBC, urinalysis, U&Es, creatinine.**

### Administration

The tablets should be ingested on an empty stomach ½–1 hour before breakfast or any other food of the day. Penicillamine can bind to calcium, iron, or zinc ions, so that less of it will be available for absorption. Antacids, or medication containing Ca++, Fe++, or Zn, should thus be avoided for at least 2 hours after ingesting penicillamine.

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

**Time to response:** 3–6 months.

### Precautions and contraindications

Penicillamine is contraindicated in SLE.

### Potential drug interactions

Antacids, iron and zinc.

### Side-effects

**Haematological:** Neutropenia, thrombocytopenia, and rarely aplastic or haemolytic anaemias.

**Renal:** Proteinuria, which may rarely progress to nephrotic syndrome, and haematuria.

**Gastrointestinal:** Nausea, taste alterations (metallic taste, usually settles spontaneously).

**Mucocutaneous:** Rashes, urticaria, oral ulceration, exfoliative dermatitis, epidermolysis bullosa, pemphigus.

**Other:** Drug-induced SLE and myasthenia gravis, Goodpasture’s syndrome, Stevens–Johnson syndrome.

### 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:

| \( \text{WBC} < 4.0 \times 10^9/l \) | Withhold until discussed with rheumatologist. |
| \( \text{Neutrophils} < 2.0 \times 10^9/l \) | Withhold until discussed with rheumatologist. |
| \( \text{Platelets} < 150 \times 10^9/l \) | Withhold until discussed with rheumatologist. |
| >1+ proteinuria on >1 occasion | Withhold until discussed with rheumatologist. |
| >1+ haematuria on >1 occasion | Withhold until discussed with rheumatologist. |
| Rash or oral ulceration | Withhold until discussed with rheumatologist. |
| Alteration of taste | Continue treatment (usually settles spontaneously). |
| Dyspepsia | Most likely due 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)**

**Sodium aurothiomalate** (intramuscular gold) modifies the immune response in inflammatory arthritis, but its mechanism of action is not understood.

**Pre-treatment assessment:** FBC, urinalysis, U&Es, creatinine, LFTs.

**Administration:** By deep intramuscular injection followed by gentle massaging of the area.

A **typical dose regimen** may be: 10 mg test dose (which should be given in the clinic followed by 30 minutes observation), followed by weekly injections of 50 mg until significant response. Thereafter either 50 mg monthly or 50 mg fortnightly for 3 months, 50 mg weekly for 3 months, and then 50 mg monthly. If after a total dose of 1 g (i.e. 20 injections) has been administered no response has occurred treatment should be stopped.

**Time to response:** About 3 months, i.e. after 10–12 injections.

**Precautions and contraindications:** Sodium aurothiomalate is contraindicated in patients with known renal or hepatic failure or SLE.

**Side-effects:**
- **Mucocutaneous:** Mild rashes but intensely itchy, rarely severe erythematous rashes and exfoliative dermatitis, photosensitivity. Irreversible skin pigmentation with prolonged treatment.
- **Haematological:** Neutropenia, thrombocytopenia, eosinophilia and rarely aplastic anaemia.
- **Renal:** Proteinuria, which may rarely progress to nephrotic syndrome, and haematuria.
- **Gastrointestinal:** Nausea, reversible taste disturbance (metallic taste), mouth ulcers, diarrhoea.
- **Other:** Rarely, cholestatic hepatitis (usually in early treatment), colitis and pulmonary fibrosis.

**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 <4.0 x 10⁹/l  Withhold *until discussed* with rheumatologist.
- Neutrophils <2.0 x 10⁹/l  Withhold *until discussed* with rheumatologist.
- Platelets <150 x 10⁹/l  Withhold *until discussed* with rheumatologist.
- >1+ proteinuria on >1 occasion  Withhold *until discussed* with rheumatologist.
- Rash or oral ulceration  Withhold *until discussed* with rheumatologist.
- 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.
SULFASALAZINE (Salazopirin EN)

**Sulfasalazine** modifies the inflammation of RA, but its mechanism(s) of action are unknown.

**Pre-treatment assessment:** FBC, LFTs.

**Administration:** The tablets should be taken with or after food, but not taken 2 hours before or after antacids or iron tablets, as they interfere with DMARD absorption.

**A typical dose regimen may be:** 500 mg/day increasing by 500 mg weekly to 2–3 g/day.

**Time to response:** Approximately 3 months.

**Precautions and contraindications:** Sulfasalazine is contraindicated in patients with known hypersensitivity to sulphonamides or salicylates. Do not use in children.

**Potential drug interactions:** Digoxin.

**Side-effects:**

*Haematological:* Neutropenia, thrombocytopenia and rarely haemolytic or aplastic anaemias.

*Hepatic:* Allergic hepatitis causes liver dysfunction early on, when dosage being increased.

*Gastrointestinal:* Mild nausea common early on, but severe nausea and vomiting may preclude drug’s use.

*Mucocutaneous:* Photosensitisation, erythematous pruritus, especially early in treatment; desensitisation kits are available from the manufacturer. Rarely exfoliative dermatitis and Stevens–Johnson syndrome can occur.

*Other:* Mild headaches with nausea early on, usually settle within a few days. More severe headaches may preclude use. Peripheral neuropathy and reversible oligospermia may occur. The dye present in sulfasalazine tablets causes a characteristic orange-yellow discoloration of urine and tears. Patients therefore need to be warned that taking the drug may stain undergarments and permanently stain extended-wear soft contact lenses (daily-wear soft contact lenses and gas-permeable lenses respond to standard cleansing). Long-term clinical usage and experimental studies have failed to show any teratogenic hazards, so drug use can continue in pregnancy.

**Monitoring:** FBC fortnightly and LFTs (incl. AST or ALT) 4-weekly for the first 12 weeks. FBC and LFTs (incl. AST or ALT) 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:**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC &lt;4.0 x 10^9/l</td>
<td>Withhold <em>until discussed</em> with rheumatologist.</td>
</tr>
<tr>
<td>Neutrophils &lt;2.0 x 10^9/l</td>
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<tr>
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</tr>
<tr>
<td>&gt;2-fold rise in AST, ALT or Alk Phos (from upper limit of reference range)</td>
<td>Withhold <em>until discussed</em> with rheumatologist.</td>
</tr>
<tr>
<td>Rash or oral ulceration normal</td>
<td>Withhold <em>until discussed</em> with rheumatologist.</td>
</tr>
<tr>
<td>MCV &gt;105fl</td>
<td>Investigate and if B12 or folate low start appropriate supplementation.</td>
</tr>
<tr>
<td>Nausea/dizziness/headache</td>
<td>If possible continue; may have to reduce dose or stop if symptoms severe.</td>
</tr>
<tr>
<td>Abnormal bruising or sore throat</td>
<td>Withhold until FBC result available.</td>
</tr>
</tbody>
</table>

**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.**
ACKNOWLEDGEMENTS
The Arthritis Research Campaign is grateful to the British Society for Rheumatology for permission to reproduce its ‘National guidelines for the monitoring of second line drugs’ as part of this article.

FURTHER READING

Arthritis Research Campaign (arc). Drug information sheets. Revised annually. At time of printing there are 19 separate information sheets available.


ADDENDUM (September 2005)
Updated guidelines for the monitoring of second-line drugs are currently being prepared by the British Society for Rheumatology. These may include data about the use of biological agents which were not part of the scope of this report when it was first constructed.