Disease-modifying Antirheumatic Drugs (DMARDs)

Therapy with disease-modifying antirheumatic drugs (DMARDs) should be started as soon as the diagnosis of rheumatoid arthritis (RA) is made.\[^1\] The early use of DMARDs has been recommended in recent years to reduce disease progression and long-term disability.\[^2\] The need for early use of DMARDs is incorporated in new National Institute for Health and Care Excellence (NICE) guidance.\[^3\] Early use requires early referral in part because DMARD initiation is the province of specialists in secondary care. The optimum use of these drugs requires specialist experience and is complicated not only because of their potential toxicity, but also by the range and combination of drugs used. There are a number of new DMARDs.

The prevailing guidelines for the management of RA recommend that, once the disease has been diagnosed and its impact on the patient's life documented, DMARDs should be commenced.\[^2\] DMARDs should be part of a range of treatments from different professional disciplines. For further details see the separate article Management of Rheumatoid Arthritis.

DMARDs, broadly speaking, either affect the immune response or suppress the disease process. As well as improving the symptoms and signs of the arthritis, they may also improve the extra-articular manifestations such as vasculitis in addition to exerting systemic effects.\[^4\]

Any DMARD that has been prescribed should be recorded in a patient's notes, both written and electronic, so that all doctors prescribing for that patient will be aware of any potential interactions with other drugs. The arrangements for shared patient care (between primary and secondary care) and monitoring of patients being treated with DMARDs is based on locally agreed protocols.

Types of disease-modifying antirheumatic drugs\[^5\]

Drugs which suppress the disease process

- **Gold:**
  - Given by intramuscular injection as sodium aurothiomalate.
  - Sodium aurothiomalate is licensed for the treatment of active progressive RA.
  - Can be an effective treatment but use is restricted by severe adverse reactions (up to 5% of recipients).

- **Penicillamine:**
  - It is a chelating agent licensed for the treatment of severe active RA, including juvenile forms (and a range of other conditions, including Wilson's disease).
  - It has a similar method of action to gold and more patients are able to tolerate it, but side-effects occur frequently.
  - The rate of onset of action is slow, improvement may not be seen for three months but, in patients who have shown no benefit after a year of treatment, the drug should be discontinued.

- **Sulfasalazine:**
  - It is licensed for the treatment of RA which has failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs).
  - It has a similar action to gold.
  - It has slightly more side-effects than methotrexate.
Drugs which affect the immune process

- Chloroquine and hydroxychloroquine:
  - Hydroxychloroquine is an antimalarial agent licensed for the treatment of RA, juvenile idiopathic arthritis, discoid and systemic lupus erythematosus (SLE), and dermatological conditions caused, or aggravated, by sunlight.  
  - They are usually better tolerated than gold or penicillamine.

- Methotrexate:
  - May be used in the treatment of RA and psoriatic arthritis.
  - It is a disease-modifying agent with both anti-inflammatory and immunosuppressant activity.
  - It is also classified as an antimetabolite cytotoxic agent, and is the most common first-line agent for the early treatment of RA in the UK.

- Azathioprine:
  - It is a cytotoxic drug and a prodrug of mercaptopurine.
  - It is used as an immunosuppressant for many autoimmune conditions and to suppress transplant rejection.
  - It acts in a similar manner to methotrexate but is usually reserved as second-line due to its toxicity.

- Ciclosporin:
  - It is a powerful immunosuppressant that appears to act specifically on lymphocytes (mainly helper T cells) resulting in depression of the cell-mediated immune response.
  - Unlike cytotoxic immunosuppressants (such as cyclophosphamide) it has little effect on bone marrow.
  - It is licensed for the treatment of severe active RA when the usual second-line therapy is inappropriate or ineffective.

- Leflunomide:
  - Leflunomide has antiproliferative properties.
  - It is licensed for the treatment of adults with active RA and also for active psoriatic arthritis.
  - It is used in the treatment of moderate-to-severe active RA, often in combination with methotrexate.

Anti-tumour necrosis factor or biological agents

The term biological agents encompasses tumour necrosis factor (TNF)-alpha-blockers (infliximab, etanercept, and adalimumab) and other agents, including abatacept, anakinra, and rituximab.

- A revolution has occurred in treating RA, due to the realisation that the proinflammatory cytokine TNF-alpha plays a central role. In a period of 10 years several agents have been developed that block this molecule and TNF inhibitors significantly improve symptoms and reduce disease activity and joint inflammation.
- The initiation and monitoring of these drugs is very much the province of the specialist. However, it is important for generalists and members of the multidisciplinary team (MDT) to be aware of how they are used and of monitoring issues.
- Infliximab (Remicade®) and etanercept (Enbrel®) are very effective in reducing the symptoms and signs of RA in patients who fail to respond to DMARDs and both reduce joint swelling, radiological erosions, malaise and fatigue.
- Clinical effectiveness and side-effect profiles are similar for all these drugs. All have rapid onsets of action - days to weeks.
- A meta-analysis has concluded that this group of drugs is very effective in the treatment of RA, both in treatment-naive and methotrexate-resistant patients.
- Contra-indications and monitoring - see individual drug monographs.
- Initiation of treatment - patients at risk of infection (those on high-dose steroids or with uncontrolled diabetes) are excluded from treatment. See also individual drug monographs.
• Complications and reasons to discontinue drug: side-effects are generally minor and tolerable. Severe adverse events are unusual but have been reported. However:
  • TNF is a key regulator of immunity, and opportunistic infections may occur.
  • There is an increased risk of tuberculosis, or reactivation of latent tuberculosis, during treatment with tumour necrosis factor alpha (TNF-alpha) inhibitors.
  • Tuberculosis in patients receiving TNF-alpha inhibitors can be life-threatening, and deaths from tuberculosis have occurred in these patients.
  • All patients should be screened before starting treatment and monitored closely during treatment.
  • Worsening of demyelinating disease, suppression of bone marrow and a variety of unusual idiosyncratic side-effects may also occur.

Choosing the right DMARD
Methotrexate should be part of the initial treatment strategy in patients with active RA. In cases of contra-indications or early intolerance to methotrexate, sulfasalazine or leflunomide should be considered as part of the initial treatment strategy.[1] An anti-TNF-alpha drug such as etanercept or infliximab may also be used in combination.

There is a stronger evidence base for the disease-modifying effects of methotrexate, sulfasalazine, leflunomide and intramuscular gold than for hydroxychloroquine, penicillamine, oral gold, ciclosporin or azathioprine, although these agents do improve symptoms and some objective measures of inflammation.[11]

The choice of first agent or combination of agents should be based on a risk/benefit analysis for individual patients.
Contra-indications

The choice of first agent or combination of agents should be based on a risk/benefit analysis for individual patients. In general these medicines should not be prescribed during pregnancy or breast-feeding unless advised by a specialist.

(These are main contra-indications - see individual drug monographs for full list of contra-indications and precautions)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Contra-indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold - sodium aurothiomalate</td>
<td>Severe liver disease, severe kidney disease, Bone marrow aplasia, history of blood disorders, Exfoliative dermatitis, Necrotising enterocolitis, Porphyria, SLE, Pulmonary fibrosis</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Moderate-to-severe kidney disease, SLE</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Salicylate hypersensitivity</td>
</tr>
<tr>
<td>Chloroquine and hydroxychloroquine</td>
<td>Pre-existing retinopathy</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Hepatic impairment, Active infection, Immunodeficiency syndromes</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Hypersensitivity to azathioprine</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Renal impairment, Uncontrolled hypertension, Uncontrolled infections, Malignancy</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Severe immunodeficiency, Serious infection, Liver dysfunction, Severe hypoproteinaemia</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Severe infections</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Active infection</td>
</tr>
</tbody>
</table>
Initiation of treatment

Due to their potential toxicity, treatment with these drugs is only initiated by specialist rheumatologists, and it is therefore essential to ensure that all patients and their GPs receive, from the specialist clinic, a clear protocol for any dosage increments and requirements for routine testing. It is also important for the practice staff to have a copy of the protocol, and a system in place for ensuring that it has been adhered to.

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold - auranofin or sodium aurothiomalate</td>
<td>Urine testing for protein and blood&lt;br&gt;U&amp;E with white cell count (WCC) differential and platelets&lt;br&gt;LFTs</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Urine testing for protein and blood&lt;br&gt;FBC and platelets&lt;br&gt;U&amp;Es</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>FBC&lt;br&gt;U&amp;Es&lt;br&gt;LFTs</td>
</tr>
<tr>
<td>Chloroquine and hydroxychloroquine</td>
<td>U&amp;Es&lt;br&gt;LFTs&lt;br&gt;Optometry assessment if visual impairment or eye disease (can cause retinopathy)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>FBC&lt;br&gt;U&amp;Es&lt;br&gt;LFTs&lt;br&gt;Urine testing for protein and blood</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>FBC and platelets</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>U&amp;Es on two occasions&lt;br&gt;Serum creatinine on two occasions&lt;br&gt;LFTs&lt;br&gt;Urine testing for protein and blood&lt;br&gt;Blood pressure (BP) measurement</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Pregnancy test&lt;br&gt;FBC&lt;br&gt;LFTs&lt;br&gt;BP measurement</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Exclude active or latent TB (tuberculin skin test and CXR)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Exclude active or latent TB (tuberculin skin test and CXR)&lt;br&gt;FBC if history of blood dyscrasia suspected</td>
</tr>
</tbody>
</table>
Monitoring \cite{5, 12}

The use of DMARDs is limited by potentially serious side-effects, and therefore patients who are taking these drugs should be monitored on a regular basis as in the table below. Note throughout that, whilst absolute values are useful indicators, trends are also important. Hence, any rapid fall or consistent downward trend in any parameter warrants extra vigilance. A useful quick reference guide has been produced by the British Society for Rheumatology. \cite{13}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Monitoring Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillamine</td>
<td>FBC and stick testing of urine two-weekly until dose is stable for three months, and then monthly.</td>
</tr>
<tr>
<td>Gold - intramuscular</td>
<td>FBC and urinalysis at the time of each injection.</td>
</tr>
<tr>
<td>Chloroquine and hydroxychloroquine</td>
<td>Annual review by an optometrist, or by enquiring about visual symptoms, rechecking visual acuity, and assessing for blurred vision using a reading chart.</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>FBC and LFTs fortnightly for the first three months, monthly for the second three months and then three-monthly and when clinically indicated. Renal function should be monitored monthly for the first three months, and as clinically indicated thereafter.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>FBC fortnightly until six weeks after last dose increase; provided it is stable, monthly thereafter until the dose and disease are stable for one year. Thereafter, monitoring may be reduced in frequency, based on clinical judgement. LFTs three-monthly. U&amp;Es 6- to 12-monthly (more frequently if there is any reason to suspect deteriorating renal function).</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>FBC and LFTs weekly for six weeks and continue every two weeks until dose is stable for six weeks; then monthly. If maintenance dose is achieved and stable for six months, consider discussing with the person to reduce monitoring to three-monthly. Repeat after dose change, and then monthly. U&amp;Es six-monthly.</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>FBC and LFTs monthly for the first six months; then every eight weeks. U&amp;Es every two weeks until dose and trend are stable for three months, and then monthly. Watch when an NSAID is added, particularly diclofenac.</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>FBC, LFTs every month for six months and, if stable, two-monthly thereafter.</td>
</tr>
<tr>
<td>Infliximab</td>
<td>First two hours - monitor for acute hypersensitivity reactions (e.g., chest pain, fever, hypotension, pruritis). Monitor for latent TB during treatment and for six months afterwards. FBC, ESR, LFTs and U&amp;Es monthly.</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Advise patients to report the development of any symptoms of TB or blood dyscrasias after treatment. FBC, ESR, LFTs and U&amp;Es monthly.</td>
</tr>
</tbody>
</table>

Complications and reasons to discontinue drugs \cite{5}

Although some have greater tendency than others, all DMARDs have a potential to cause myelosuppression. Many also cause renal or liver toxicity, skin rash, or gastrointestinal disturbance. \cite{6}

Patients should be warned to report any warning symptoms or signs as detailed below:

**Symptoms of myelosuppression**
- Sore throat
- Fever and other signs of infection
- Unexpected bleeding or bruising
- Purpura and rashes
- Mouth ulcers
- Cough or breathlessness
Further reading & references

- BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids; British Society for Rheumatology (2016)
- BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs; British Society for Rheumatology (2017)

1. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update; European League Against Rheumatism (Dec 2013)
3. Rheumatoid arthritis in adults: management; NICE Clinical Guideline (February 2009)
4. Management of early rheumatoid arthritis; Scottish Intercollegiate Guidelines Network - SIGN (February 2011)
5. DMARDs; NICE CKS, January 2013
6. British National Formulary
7. Rheumatoid arthritis - adalimumab, etanercept and infliximab; NICE Technology Appraisal Guidance, October 2007
13. Quick reference guideline for monitoring of disease-modifying anti-rheumatic drug (DMARD) therapy; British Society for Rheumatology (November 2009)

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