Disease-modifying Antirheumatic Drugs (DMARDs)

Indications and use

Disease-modifying antirheumatic drugs (DMARDs) are a group of drugs which alter the outcome or course of inflammatory conditions. Indications include:

- Rheumatoid arthritis (RA).
- Psoriasis.
- Psoriatic arthritis.
- Systemic lupus erythematosus and vasculitic conditions.
- Juvenile idiopathic arthritis (JIA).
- Ulcerative colitis.
- Crohn’s disease.
- Ankylosing spondylitis.
- Granulomatosis with polyangiitis.

DMARDs are most widely used in the treatment of rheumatoid arthritis. Therapy with DMARDs should be started as soon as the diagnosis of RA is made, and ideally within three months of the start of persisting symptoms. Management of RA has radically changed over the past 30 years as evidence grew to support efficacy of DMARDs in improving outcomes. The aim became disease modification rather than symptom control alone. Early use of DMARDs is now recommended in order to reduce disease progression and long-term disability. 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. Although DMARDs are key and are first-line, they should be part of a range of treatments from different professional disciplines. For further details see the separate Management of Rheumatoid Arthritis article.

DMARDs, broadly speaking, either affect the immune response or suppress the disease process. As well as improving the symptoms and signs of joint disease, they may also improve the extra-articular manifestations of the conditions they treat.

The arrangements for shared patient care (between primary and secondary care) and monitoring of patients being treated with DMARDs are based on locally agreed protocols. Once a patient is stabilised on DMARDs, GPs may be asked to continue prescribing and monitoring as part of an agreed shared care protocol. Most DMARDs require regular blood test monitoring. Individual monitoring requirements are discussed in the relevant section below.

Types of disease-modifying antirheumatic drugs

Broadly, DMARDs are categorised as:

- **Conventional DMARDs (cDMARDs) or non-biological DMARDs.** These include methotrexate, leflunomide, sulfasalazine and hydroxychloroquine. For RA, these are recommended as the first-line treatment, and more than one may be given in combination. Others include gold (sodium aurothiomalate), azathioprine, ciclosporin and penicillamine.
- **Biologic and targeted synthetic DMARDs.** These are used in severe conditions where intensive treatment with cDMARDs has not suppressed the disease, and may be given in combination with a cDMARD. Biologics include:
  - Anti-tumour necrosis factor (anti-TNF) agents - such as adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab.
  - Other biologic agents, including abatacept, anakinra, belimumab, ixekizumab, rituximab, secukinumab, tocilizumab, and ustekinumab.
  - Targeted synthetic (ts) DMARDs - the Janus kinase (Jak) inhibitors tofacitinib and baricitinib.

General principles for use of disease-modifying antirheumatic drugs

- Initiation of DMARDs and stabilisation should be in the hands of a specialist, but GPs may then be asked to take on monitoring and prescribing. This should always be on the basis of an agreed written shared-care protocol. Individual medicines have different requirements, and national and local protocols may vary.
- All DMARDs other than hydroxychloroquine require regular blood tests. DMARDs are frequently given in combination with other DMARDs. If a person is on more than one, then monitor at intervals of the one which requires the most frequent blood tests. Trends may be as important as absolute values.
- Be aware of interactions with other medication.
- People on DMARDs are more prone to infections and complications of infections. There is also more risk of toxicity during intercurrent illness, particularly where renal function is affected.
Live vaccines (e.g., MMR, oral typhoid, yellow fever) are contra-indicated for people on DMARDs, but offer routine vaccination with non-live vaccines against common infections. Flu vaccine should be given annually and pneumonia vaccination prior to starting the DMARD then 10-yearly (or 5-yearly if started after the DMARD). Herpes zoster vaccination should be given to those aged over 50 years prior to starting biologic DMARDs if there are no contra-indications (such as recent steroid use or recent use of certain cDMARDs). Varicella-zoster vaccination may also be offered if there is no history of chickenpox and an antibody test is negative. Both zoster vaccines are live and can only be given in certain circumstances to people on DMARDs - it depends on the class of DMARD and the dose in some cases - consult a specialist or the British Society for Rheumatology guidelines cited above.

People on DMARDs should be made aware of potential adverse effects, and know who to contact should these develop.

Specialists are advised to screen for tuberculosis (TB), hepatitis B, hepatitis C and also HIV where risk factors are present prior to starting a biologic DMARD. Other general baseline investigations are also required, and these medicines are not started during an active infection.

The choice of first agent or combination of agents should be based on a risk/benefit analysis for individual patients, in line with recommendations in National Insitute for Health and Care Excellence (NICE) and specialist guidelines. In general these medicines are not usually prescribed during pregnancy or breastfeeding. Knowledge of adverse effects in these situations is limited; however, some are thought to be safe, and the British Society of Rheumatology has produced guidelines with specific recommendations for specialists.

Those on biologic DMARDs should be reviewed in a specialist department at least once every six months.

There is now a bewildering array of DMARDs, and the non-specialist cannot hope to be familiar with them all. It is therefore important to familiarise oneself with the individual shared-care protocol information for each patient on a DMARD in order to prescribe safely. A few specifics on the more commonly used DMARDs:

- **Methotrexate** is usually used first-line, particularly in RA, and therefore most GPs will be involved in prescribing or monitoring it. Methotrexate is usually given once a week, not daily. Folic acid is usually co-prescribed (also weekly) to reduce toxicity and adverse effects. Monitoring requirements are listed below.

- **Hydroxychloroquine** does not require regular blood tests routinely; however, people taking it should have a baseline ophthalmic examination in a hospital eye department, ideally with a colour retinal photograph and spectral domain optical coherence tomography (SD-OCT) scans of the macula [7]. After five years of therapy they should be referred for annual repeat hospital clinic review. This is due to the risk of retinopathy on this medication, the prevalence of which in long-term use patients is around 7.5%. This is dependent on dose and duration of use but can increase to 20-50% after 20 years of therapy. The only way of preventing further damage, if detected, is to stop the medication. Risk is higher if the person is also taking tamoxifen.

- **Gold** is given as sodium aurothiomalate by deep intramuscular injection and the area gently massaged. A test dose must be given followed by doses at weekly intervals until there is evidence of remission. In patients who do respond, the interval between injections is then gradually increased to four weeks and treatment is continued for up to five years after complete remission [8].

- **NICE guidance allows the use of numerous biologic DMARDs** for RA where disease is severe, where it has not responded to intensive treatment with a combination of cDMARDs, and where the companies provide them within the agreement of the patient access schemes, and sets out the order in which they should be tried. Numerous NICE technology appraisal (TA) guidance documents on individual biologics or groups of them are summarised in the NICE pathway ‘Drug treatment for rheumatoid arthritis’ [9].

Monitoring [1, 8]

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. The monitoring requirements and plan should be set out in the written shared care protocol for each patient.
<table>
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<tr>
<th>Drug Type</th>
<th>Monitoring Requirements</th>
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| Penicillamine | - FBC, renal function, LFT, urinalysis (for blood and protein).  
- Two-weekly until dose stable for six weeks, then monthly.  
- Once stable for a year, consider reducing to three-monthly.  
- If dose is increased, monitor every two weeks until stable for six weeks, then revert to previous schedule.  
- Watch for platelet and WBC falls. |
| Gold - intramuscular | - FBC, renal function, LFT, urinalysis (for blood and protein).  
- Two-weekly until dose is stable for six weeks.  
- Then monthly for three months.  
- Thereafter at least every 12 weeks (more frequent if higher risk of toxicity).  
- If dose is increased, monitor every two weeks until dose is stable for six weeks, then revert to previous schedule. |
| Chloroquine and hydroxychloroquine | - Following baseline eye clinic imaging, annual review after being on therapy for five years. No routine laboratory test monitoring required. |
| Sulfasalazine | - FBC, renal function, LFTs.  
- Two-weekly until dose is stable for six weeks.  
- Then monthly for three months.  
- Thereafter at least every 12 weeks (more frequent if higher risk of toxicity).  
- After 12 months, monitoring may be stopped.  
- If dose is increased, monitor every two weeks until dose is stable for six weeks, then revert to previous schedule. |
| Methotrexate | - FBC, renal function, LFTs.  
- Two-weekly until dose is stable for six weeks.  
- Then monthly for three months.  
- Thereafter at least every 12 weeks (more frequent if higher risk of toxicity).  
- If dose is increased, monitor every two weeks until dose is stable for six weeks, then revert to previous schedule. |
| Azathioprine | - FBC, renal function, and LFTs.  
- Two-weekly until dose is stable for six weeks.  
- Then monthly for three months.  
- Thereafter at least every 12 weeks (more frequent if higher risk of toxicity).  
- If dose is increased, monitor every two weeks until dose is stable for six weeks, then revert to previous schedule. |
| Ciclosporin | - FBC, renal function, LFTs, blood glucose, blood pressure.  
- Every two weeks until dose is stable for six weeks.  
- If stable for 12 months, consider reducing monitoring to three-monthly.  
- Monitor more frequently if higher risk of toxicity.  
- If dose is increased, monitor every two weeks until dose is stable for six weeks, then revert to previous schedule. |
| Leflunomide | - FBC, renal function, LFTs, blood pressure, weight.  
- Two-weekly until dose is stable for six weeks.  
- Then monthly for three months.  
- Thereafter at least every 12 weeks (more frequent if higher risk of toxicity).  
- If dose is increased, monitor every two weeks until dose is stable for six weeks, then revert to previous schedule. |
| Biologics | - FBC, U&E, creatinine, LFT at 3-4, then every six months.  
- Lipids 4-8 weeks after starting treatment.  
- Assess for signs of infection before each injection/infusion.  
- Monitoring of subcutaneous biologics often done in secondary care and as patients are often on cDMARDs such as methotrexate also, the primary care monitoring may be confined to that. |
| Targeted synthetic DMARDs - baricitinib and tofacitinib | - FBC, renal function, and LFTs.  
- Two-weekly until dose is stable for six weeks.  
- Then monthly for three months.  
- Thereafter at least every 12 weeks (more frequent if higher risk of toxicity).  
- If dose is increased, monitor every two weeks until dose is stable for six weeks, then revert to previous schedule.  
- Also lipids after 12 months, then periodically, and TB if clinically indicated. |

As well as where there are concerning trends, blood results which should prompt immediate discussion with the specialist team whilst withholding the DMARD include:

- WBC <3.5 x 10^9/L
- Neutrophils <1.6 x 10^9/L
- Eosinophils >0.5 x 10^9/L
Complications and reasons to discontinue drugs

Although some have greater tendency than others, all DMARDs have a potential to cause myelosuppression. Many also cause renal or liver toxicity, pulmonary problems, skin rashes, or gastrointestinal disturbance. There may be an increased risk of skin cancers with anti-TNF medication; evidence is conflicting. Patients should be advised of the need for sun protection, skin surveillance and prompt reporting of new persistent skin lesions. There is no conclusive evidence of an increased risk of solid tumours or lymphoproliferative conditions with biologic DMARDs, but surveillance is ongoing as they are a relatively new class of medication. Anti-TNF therapy may potentially worsen or cause demyelinating disease and is not used in those with a history of multiple sclerosis, and is withdrawn if demyelination occurs.

Patients should be warned to report any warning symptoms or signs of blood disorders, liver toxicity or respiratory problems such as those detailed below:

- Sore throat.
- Fever and other signs of infection.
- Unexpected bleeding or bruising.
- Purpura and rashes.
- Mouth ulcers.
- Cough or breathlessness.
- Peripheral neuropathy.
- Nausea or vomiting.
- Abdominal pain.
- Dark urine.

If a person on DMARDs develops any of these symptoms, consult a specialist urgently, and consider stopping the medication.

If a person on a biologic DMARD develops any of the following, the medication should be stopped and they should be referred urgently to rheumatology:

- Symptoms of possible TB (cough, haemoptysis, or weight loss).
- Signs or symptoms of heart failure, or worsening heart failure.
- Symptoms of possible interstitial lung disease (such as shortness of breath or dry cough).
- Skin rashes.
- Severe abdominal pain, or unexplained change in bowel habits accompanied by fever.

Further reading & references

1. DMARDs; NICE CKS, July 2018 (UK access only)
2. Rheumatoid arthritis in adults: management; NICE Guideline (July 2018)
4. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs; British Society of Rheumatology (BSR), June 2017
5. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis, August 2018
6. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding - Part I: standard and biological disease modifying anti-rheumatic drugs and corticosteroids; British Society of Rheumatology, January 2016
7. Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on Screening, Clinical Guideline from the Royal College of Ophthalmologists, February 2018
8. British National Formulary (BNF); NICE Evidence Services (UK access only)
9. Drug treatment for rheumatoid arthritis; NICE Pathway, July 2018

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