Prescribing and monitoring non-biological DMARDs

STEVE CHAPLIN

The British Society for Rheumatology and British Health Professionals in Rheumatology (BSR/BHPR) recently updated their guidance on prescribing and monitoring non-biological disease-modifying antirheumatic drugs (DMARDs) for patients with rheumatic disease. This article provides an overview of the main recommendations of the new guideline.

When medicines are introduced, they tend to draw the focus of scientific and clinical attention away from the old and familiar to what is new and exciting. Biological disease-modifying antirheumatic drugs (DMARDs) are a case in point and the spotlight has recently spared the older non-biological DMARDs. This has now been rectified with the publication of a new evidence-based guideline from the British Society for Rheumatology and British Health Professionals in Rheumatology (BSR/BHPR) on the use of non-biological DMARDs in rheumatic disease.¹

Overview

The guideline, an update to the BSR/BHPR 2008 document, describes measures to ensure safe prescribing of non-biological DMARDs in adults (>16 years old), covering pretreatment screening, the impact of co-morbidities, monitoring for toxicity, treatment during intercurrent illness or surgery, and shared care guidelines. It is intended for all healthcare professionals involved in the care of patients with rheumatic disease in primary and secondary care; it is also for patients (the authors included a patient representative), though they will probably find the executive summary² more accessible than the full guideline summarising the evidence base.

The guideline covers 12 agents: apremilast, azathioprine, ciclosporin, hydroxychloroquine, leflunomide, mepacrine, methotrexate, minocycline, mycophenolate mofetil, sodium aurothiomalate (gold), sulfasalazine and tacrolimus. It does not consider their indications or drug interactions, nor does it cover biological DMARDs, new non-biological DMARDs such as the janus kinase (JAK) inhibitors, treatment in the under-16s, or prescribing for women who are pregnant or breastfeeding (most of which is covered in separate guidelines).

Pretreatment and initiating DMARDs

Some measures are recommended before prescribing any DMARD (see Table 1). Although the guideline provides supporting evidence, several need no justification (eg the value of...
specialist supervision) and others are recommended in NICE guidance. The co-morbidities most relevant to prescribing a DMARD are cardiovascular, liver and kidney disorders.

Taking a history of respiratory symptoms and respiratory examination is recommended for all patients. The extent of screening for lung disease should be determined by the patient’s characteristics not the DMARD most likely to be prescribed. People with rheumatoid arthritis have a lifetime risk of interstitial lung disease of 10% and the risk is greater in other connective tissue disorders. Furthermore, smoking is a shared risk factor for lung disease and rheumatoid arthritis. Patients in whom parenchymal lung disease is suspected should undergo lung function testing and appropriate imaging (chest radiograph with or without high-resolution CT imaging) and be considered for referral to a respiratory specialist. Current smokers should be offered smoking cessation services.

Patients should be screened for hepatitis B and C and for HIV infection. DMARDs can reactivate hepatitis B (little is known about their impact on hepatitis C) and may increase the risk of infection for people living with HIV.

People with rheumatic disease who are taking a DMARD are included in the group of under-65s considered at risk and who should receive vaccination. This is the responsibility of primary care but uptake among people with rheumatic disease is low. Ideally, pneumococcal vaccine should be administered before starting a DMARD; individuals who are severely immunocompromised require a different schedule (as set out in The Green Book).

Live vaccines are normally avoided in immunocompromised individuals and this includes those travelling to areas where yellow fever is prevalent. A low level of immunosuppression (eg standard-dose DMARDs, prednisolone up to 20mg daily) is not considered an absolute contraindication to vaccination but clinician discretion is advised. People with rheumatic diseases are at increased risk of shingles but there is no recommendation to offer the vaccine below the usual age threshold of 69 years.

There are also specific measures to take before prescribing some DMARDs. All patients to be treated with methotrexate should take folic acid 5mg weekly (taken on a different day from methotrexate); thiopurine methyltransferase status should be assessed before prescribing azathioprine (0.3% of people have low activity and cannot metabolise azathioprine); and a formal ophthalmic examination including objective retinal assessment (not simple visual acuity tests) should be carried out within one year of starting treatment with hydroxychloroquine.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Accumulates in renal failure</th>
<th>Nephotoxic</th>
<th>GFR category*</th>
<th>Recommended adjustment (% standard dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apremilast</td>
<td>yes</td>
<td>no</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>no</td>
<td>no</td>
<td>normal dose</td>
<td>75–100</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>no</td>
<td>yes</td>
<td>normal dose</td>
<td></td>
</tr>
<tr>
<td>Sodium aurothiomalate</td>
<td>yes</td>
<td>no</td>
<td>no data</td>
<td>avoid</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>yes</td>
<td>no</td>
<td>75</td>
<td>25–50</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>no</td>
<td>no</td>
<td>normal dose</td>
<td>use with caution</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>yes</td>
<td>yes</td>
<td>50</td>
<td>contraindicated</td>
</tr>
<tr>
<td>Minocycline</td>
<td>yes</td>
<td>no</td>
<td>use with caution</td>
<td>contraindicated</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>yes</td>
<td>no</td>
<td>normal dose</td>
<td>max 1g twice daily</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>not stated in SPC</td>
<td>no</td>
<td>normal dose</td>
<td>use with caution</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>no</td>
<td>yes</td>
<td>use with caution</td>
<td>contraindicated</td>
</tr>
</tbody>
</table>

* Calculated glomerular filtration rate (GFR) in ml/min/1.73m². See NICE guideline CG182 for new GFR categories of chronic kidney disease.³ NB. Categories G1–G5 have the same GFR thresholds as the old chronic kidney disease stages 1 to V.

Table 2. Recommended dose adjustment for DMARDs in chronic kidney disease, according to the summaries of product characteristics¹
Co-morbidities

Co-morbidities are generally not an absolute contraindication to DMARD treatment but there is a need for caution. Drugs associated with pneumonitis (most DMARDs are, though the risk with methotrexate has been overestimated) should be used with care in patients with poor respiratory reserve. The underlying cause of abnormal liver biochemistry should be sought and treated before prescribing a DMARD. If viral hepatitis is evident, a DMARD with low immunosuppression risk such as hydroxychloroquine or sulfasalazine may be preferred. Extreme caution is advised in patients with impaired liver synthetic function (e.g. cirrhosis), who are at greater risk of toxicity; sulfasalazine may be an option in such cases.

Most DMARDs undergo some renal excretion, and patients with chronic kidney disease often require dose reduction and more frequent monitoring. Table 2 summarises the manufacturers’ recommendations for dose adjustment, depending on the stage of chronic kidney disease.

Cardiovascular disease is not a contraindication to DMARD therapy: treatment of rheumatoid arthritis – notably with methotrexate, leflunomide or sulfasalazine – is associated with a reduction in cardiovascular risk. The risk of new cancers during DMARD treatment is no greater than in the population at large. Prior malignancy is generally not a contraindication but evidence is limited and there are exceptions: lymphoproliferative disorder induced by methotrexate is a clear contraindication to further treatment and a patient with skin cancer should be monitored by a dermatologist. The risk should be assessed individually for each patient.

Monitoring

The guideline recommends a standard schedule for monitoring patients newly prescribed a DMARD or when a second DMARD is initiated (see Table 3) but again there are many exceptions. No routine monitoring is necessary with apremilast, hydroxychloroquine, methotrexate or minocycline. Standard monitoring is recommended for azathioprine, sodium aurothiomalate, leflunomide and mycophenolate mofetil, and for 12 months for sulfasalazine.

Monthly monitoring should be extended long-term for ciclosporin, methotrexate plus leflunomide and tacrolimus but less frequent monitoring can be considered for patients who have been stable for 12 months. There are also recommendations for additional monitoring for ciclosporin and tacrolimus (blood pressure and glucose at every visit), leflunomide (blood pressure and weight at every visit), sodium aurothiomalate (urinalysis for blood and protein before each dose) and when hydroxychloroquine is taken for more than five years (annual eye assessment, ideally including optical coherence tomography).

Therapeutic drug monitoring is useful with ciclosporin and tacrolimus but, compared with the transplantation setting, the doses used in rheumatology are smaller and blood levels have not been correlated with efficacy; monitoring frequency may therefore be lower.

Perioperative management

Most patients who undergo arthroplasty are being treated with a DMARD and/or a steroid at the time. The decision whether to stop or continue therapy depends on the risks of a disease flare (affecting 10–20% of patients with rheumatoid arthritis) or an infection (more likely with active rheumatoid arthritis and immunosuppression). These risks vary between DMARDs and may be greater with leflunomide than methotrexate (for which there is most evidence). There is relatively little evidence on which to base a decision for other DMARDs.

The guideline recommends that DMARDs should not be stopped routinely during the perioperative period but the decision should be individualised for patients undergoing a high-risk procedure. Risk factors include longer duration surgery, class 3/4 procedures, older age, impaired renal function and co-morbidity. Steroid exposure should be minimised before surgery and it is not usually necessary to increase the dose to prevent adrenal insufficiency.

Intercurrent infection

The risk of serious infection (e.g. infection requiring intravenous antibiotics or hospitalisation) is increased in many people with inflammatory arthritis and may be greater with leflunomide than methotrexate (for which there is most evidence). There is relatively little evidence on which to base a decision for other DMARDs.

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Table 3. Standard schedule for blood monitoring when starting DMARD treatment (see text for exceptions)\(^1\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Monitoring Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>Every visit</td>
</tr>
<tr>
<td>Creatinine/calculated GFR</td>
<td>Every visit</td>
</tr>
<tr>
<td>ALT and/or AST</td>
<td>Every visit</td>
</tr>
<tr>
<td>Albumin</td>
<td>Every visit</td>
</tr>
<tr>
<td>GFR</td>
<td>Every visit</td>
</tr>
<tr>
<td>ALT and/or AST and albumin</td>
<td>Every 4 weeks</td>
</tr>
</tbody>
</table>

Table 4. Criteria for contacting the rheumatology team to consider suspending DMARD treatment under a shared care agreement\(^1\)

- White cell count <3.5 x 10⁹/L
- Mean cell volume >105fl
- Neutrophils <1.6 x 10⁹/L
- Creatinine rise >30% over 12 months and/or calculated GFR <60ml/min/1.73m²
- Unexplained eosinophilia >0.5 x 10⁹/L
- ALT and/or AST >100 U/L
- Platelet count <140 x 10⁹/L
- Unexplained reduction in albumin <30g/L

GFR = glomerular filtration rate; ALT = alanine aminotransferase; AST = aspartate aminotransferase

FBC = full blood count; GFR = glomerular filtration rate; ALT = alanine aminotransferase; AST = aspartate aminotransferase
When initiating treatment, information is available to provide to the patient on the risks and benefits of methotrexate, confirmation of understanding/consent, baseline tests conducted, the need for monitoring and the monitoring schedule. A patient-held recording document is issued and its use explained.

**Shared care guidelines should clearly state:**
- Prescribing and monitoring responsibilities
- How often will blood tests be conducted and in which location
- Which clinician will be responsible for receipt and review of the results
- Who will communicate necessary dosage changes to the patient (and to the GP if hospital reviewed for the GP prescriber)
- Who will record test results in the patient-held record document
- Trusts without shared care guidelines must make similar appropriate arrangements

**When prescribing:**
- All prescribers should avoid the use of ‘as directed’ in prescribing – a specific dose must be applied to each prescription
- Patients often understand their dose by number of tablets rather than milligrams; quantity and frequency of dose should be regularly discussed with the patient
- Repeat prescriptions should be removed from the surgery repeats pile and retained separately for prescriber review prior to authorising by signature (shading the prescription signature space on FP10 or WP10 forms to alert the prescriber to high-risk drugs might help)
- Beware patients attending with other symptoms – signs of toxicity or intolerance may present as, for example, breathlessness, dry persistent cough, vomiting and diarrhoea
- Patients receiving methotrexate may be admitted to any ward or receive outpatient treatment for co-existing conditions, and staff in all areas may therefore be involved in continuity of prescribing, monitoring or administration
- Full medicines reconciliation, conducted by pharmacists, should be undertaken on admission, and prescribing, monitoring and administration requirements recorded in the patient’s notes
- It is the prescriber’s responsibility to record the correct dosage and frequency on the hospital drug administration chart and to strike out the six days of the week when a dose must not be administered in the administration section on the chart
- Handwritten prescriptions and discharge summary information must be complete and legible and include in full the form, strength, dose and directions

Table 5. National Patient Safety Agency checklist for safe prescribing of methotrexate

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### Shared care

Treatment with a DMARD is usually initiated in secondary care and continued long-term in primary care. When this occurs, a local written shared care agreement should specify the responsibilities of the patient, the primary care team and the rheumatology team. Responsibility for ensuring adherence to monitoring guidance rests with the prescriber. Table 4 lists the criteria for urgently contacting the rheumatology team for action within one day but these should not be interpreted rigidly: trends in these parameters should also be taken into account.

Methotrexate, the most frequently prescribed DMARD, has been associated with clinically significant prescribing and administration risks and the National Patient Safety Agency has published guidance to support safer prescribing (see Table 5). This guidance also warns of the potential for confusion between the two strengths of methotrexate tablet (2.5mg and 10mg) and different devices for parenteral use.

### Summary

When expensive biological DMARDs steal the limelight, the mundane non-biologicals can be underestimated but they remain effective though potentially toxic drugs. This guideline provides a clear description of the practicalities involved in prescribing DMARDs in adults, including both general and drug-specific points for best clinical practice. It is relevant to everyone involved in using these agents, establishing the principle that care and vigilance are needed to ensure both appropriate and safe use.

### References


### Declaration of interests

None to declare.

Steve Chaplin is a medical writer specialising in therapeutics