A protocol for drugs that require regular monitoring

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The author discusses the regular monitoring requirements of the DMARDs and other drugs and provides a protocol for blood test monitoring in general practice.

For some drugs there is a need for regular monitoring to ensure appropriate dosing and reduction in the risk of adverse effects. Disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and sulfasalazine, are a group that have a long list of potentially dangerous side-effects and can only be safely used if carefully monitored. DMARDs, and other drugs such as amiodarone or lithium, have monitoring detailed in the licence requirements and manufacturer’s Summary of Product Characteristics (SPC), available from the electronic Medicines Compendium (eMC) and the British National Formulary (BNF). Prescribers need to be sure that the required monitoring has been regularly performed and that the results are normal when they sign the prescription.

Many of these drugs are initiated in secondary care but general practitioners play a very important role in ensuring that drugs continue to be used safely through drug monitoring and patient safety surveillance, often in a shared-care arrangement.

The safe use of methotrexate has been highlighted by The National Patient Safety Agency (NPSA) who have stated that oral methotrexate is a safe and effective medication if taken at the right dose and with appropriate monitoring. However, as the NPSA’s Patient Safety Alert 13 highlighted, very occasionally problems with taking the medication can cause serious harm and even death. From July 2004 to 2006, the NPSA received 165 reports of patient safety incidents involving oral methotrexate.

They state that: ‘For NHS organisations with shared-care guidelines, the following issues should be addressed: clarity of prescribing and monitoring responsibilities; how often blood tests will be conducted and in which location; which clinician will be responsible for receipt and review of the results; and who will communicate any necessary dosage changes to the patient’. The British Society for Rheumatology, British Health Professionals in Rheumatology Standards and the

KEY POINTS

- The prescriber must know that blood and urine markers are normal before signing any prescription for a DMARD or other drug that needs regular monitoring as an SPC requirement.
- By having a systematic audited procedure in place that identifies all patients prescribed drugs needing monitoring and ensuring testing as recommended, the prescriber can be confident when issuing prescriptions.
- A monitoring procedure must include both checking correct monitoring at the correct frequencies and also monthly searches to ensure all patients prescribed drugs needing regular monitoring are identified.
- A lead GP or GP group needs to be identified to oversee the on-going procedure, check test results, ensure monitoring is set up for the correct tests at the correct frequency and deal with any problems (for example non-attenders).
- A practice nurse, phlebotomist or team needs to be identified to run the monitoring scheme, ensuring patients are identified and attend for their monitoring.
- Regular audit must be part of the scheme to ensure the procedure is identifying all patients prescribed drugs needing regular monitoring and that it is ensuring all patients have the correct tests at the recommended frequencies.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Blood monitoring (SPC recommendations)</th>
<th>Suggested regular monitoring (or as local shared-care guidelines)</th>
<th>Other monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>FBC weekly for the first 4 weeks (BNF), 8 weeks (SPC) then monthly or at least every 3 months; caution in renal or hepatic impairment</td>
<td>FBC, U&amp;Es + LFTs weekly for 8 weeks after each dose increase then monthly x 4 then 3 monthly (assuming stable and no dose increase)</td>
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<tr>
<td>Chlorambucil</td>
<td>FBC before each treatment</td>
<td>FBC + U&amp;Es every 2 weeks before each treatment</td>
<td>urine tests (protein and blood) with each blood test</td>
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<tr>
<td>Ciclosporin</td>
<td>monitor kidney function, potassium, magnesium, liver function</td>
<td>FBC, U&amp;Es + LFTs 2 weekly for 8 weeks after each dose increase then monthly x 4 then 2 monthly (assuming stable and no dose increase)</td>
<td>regular monitoring of BP is required – suggest BP at each blood test; urate and lipids 3 monthly</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>use with caution in hepatic or renal impairment</td>
<td>FBC, U&amp;Es + LFTs 6 monthly</td>
<td>annual visual acuity test</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>FBC/ALT(SGPT) every 2 weeks for 6 months then every 8 weeks; impaired liver function and moderate to severe renal function are contraindications</td>
<td>FBC, U&amp;Es + LFTs 2 weekly for 6 months after each dose increase then monthly x 4 then 2 monthly (assuming stable and no dose increase)</td>
<td>BP must be checked before the start of leflunomide treatment with each blood test</td>
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<tr>
<td>Methotrexate</td>
<td>CSM advice: FBC/kidney function tests (U&amp;Es)/LFTs repeated weekly until stabilised and then every 2–3 months</td>
<td>FBC, U&amp;Es + LFTs weekly for 8 weeks after each dose increase then monthly x 4 then 3 monthly (assuming stable and no dose increase)</td>
<td></td>
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<tr>
<td>Mycophenolate</td>
<td>FBC weekly for the first 4 weeks, twice a month for 2 months then every month in the first year</td>
<td>FBC, U&amp;Es + LFTs weekly for the first 4 weeks, twice a month for 2 months, every month in the first year, then 3 monthly (assuming stable and no dose increase)</td>
<td></td>
</tr>
<tr>
<td>Myocrisin (im gold)</td>
<td>FBC before each im injection</td>
<td>FBC prior to each injection – review results prior to giving next injection</td>
<td>urine tests (protein and blood) with each blood test</td>
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<tr>
<td>Penicillamine</td>
<td>FBC monthly; caution in renal insufficiency</td>
<td>FBC every 2 weeks for 8 weeks after every dose increase then monthly</td>
<td>urine tests (protein and blood) with each blood test</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>FBC/LFTs monthly for the first 3 months, U&amp;Es at regular intervals</td>
<td>FBC, U&amp;Es + LFTs 2 weekly for 8 weeks after each dose increase then monthly x 4 then 3 monthly (assuming stable and no dose increase)</td>
<td>urine tests (protein and blood) 3 monthly</td>
</tr>
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</table>

Table 1. The SPC licence and suggested regular monitoring requirements for the DMARDs; FBC = full blood count, ALT = alanine aminotransferase, SGPT = serum glutamic-pyruvic transaminase, LFT = liver function test, U&Es = urea and electrolytes
Blood monitoring detailed in the SPC

<table>
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<th>Drug</th>
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<td>Amlodarone</td>
<td>Clinical and biological monitoring is recommended before starting the treatment in all patients. Monitoring should be carried out during treatment, at 6-monthly intervals and for several months following its discontinuation. It is advisable to monitor liver function, particularly transaminases, before treatment and 6 monthly thereafter.</td>
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<tr>
<td>Lithium</td>
<td>Lithium levels every 3 months when stable; U&amp;Es/TFTs 6–12 monthly following stabilisation of serum lithium levels, the period between subsequent measurements can be increased gradually, but should not normally exceed 2–3 months. Renal, cardiac and thyroid functions should be re-assessed regularly during treatment with lithium; BNF states U&amp;Es/TFTs 6 monthly.</td>
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<tr>
<td>Mesalazine</td>
<td>Patients on mesalazine should have renal function monitored (with serum creatinine levels measured) prior to treatment start. Renal function should then be monitored periodically during treatment, for example every 3 months for the first year, then 6 monthly for the next 4 years and annually thereafter, based on individual patient history.</td>
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Table 2. Examples of other drugs that have regular monitoring requirements in the SPCs; U&Es = urea and electrolytes, TFTs = thyroid function tests.

British Association of Dermatologists guideline for DMARD therapy (2008) states that, whatever DMARD is considered appropriate for a patient, it is paramount that the patient is carefully monitored so that there is no delay in the detection of any untoward effect of the drug; monitoring will also contribute to assessing activity of the underlying disease.5

Table 1 shows the SPC licence monitoring requirements for the DMARDs and a suggested regular monitoring schedule; most areas will have shared-care guidelines for monitoring with their local rheumatology, renal, dermatology and/or gastroenterology departments.

Table 2 gives examples of other drugs that have regular monitoring requirements.

Setting up a practice monitoring scheme

Every time a prescriber signs a prescription for a DMARD or other drug needing regular monitoring, they need to be certain that the required blood tests and other monitoring have been done within the appropriate time scale and that the results are within the normal range. By having a practice monitoring procedure, the prescriber can be confident:

- that all patients on drugs that require regular monitoring are identified
- that the correct tests have been carried out
- the tests have been done at the required frequency
- that the procedure continues to function optimally through regular auditing.

When setting up a regular monitoring scheme, it is important that the procedure ensures that both the following criteria are systematically checked:

- all patients on drugs that need regular monitoring are checked for having the correct blood and urine tests at the correct frequency
- drugs are searched for each month to ensure all patients receiving DMARDs, etc, from the practice have been included in the monitoring system.

Before starting a practice monitoring scheme, a search should be performed to look for any patients who have not had the required monitoring and get all blood tests correct and up to date. This audit will also provide a baseline for future auditing of the practice monitoring scheme.

The drugs to be included in the scheme should be agreed by the practice but should include all those that have monitoring requirements detailed in their SPC (see Tables 1 and 2). The practice might then decide to add other drugs where they feel they would like to know monitoring has been done, for example the novel oral anticoagulants (NOACs) dabigatran (Pradaxa), rivaroxaban (Xarelto) and apixaban (Eliquis) where renal function is important for dosing and on-going use.

A suggested protocol

Table 3 details an example protocol for monitoring DMARDs and other drugs in primary care; this example can be applied to any patient record system. A lead GP (or ‘DMARD group’) needs to be identified so that they can have an overview of the procedure, check blood test results, confirm monitoring and frequency for new patients and deal with any problems and queries arising.

The phlebotomist is trained to perform venepuncture, to test urine and do blood pressure checks. Both phlebotomist and lead GP/DMARD group needs to be fully aware of the Shared Care Monitoring Guidelines and know which blood and urine tests are required and the frequency of tests for each drug in question.

A recall system needs to be in place to ensure patients who have not presented for their tests will be contacted and offered appointments.

For patients who continue to be monitored by the hospital but have their drugs prescribed in primary care, the phlebotomist or practice nurse should check with the hospital (department or pathology) that monitoring has been done regularly and that the results are within the normal range. A note should be added to
**Target population**
All patients on established maintenance doses of DMARDs (azathioprine, chlorambucil, ciclosporin, hydroxychloroquine, lefunomide, methotrexate, mycophenolate, Mycrosin, penicillamine, sulfasalazine), lithium, amiodarone or mesalazine.

**Aim**
To minimise the risk and monitor for the development of any adverse effects attributable to these drugs. To highlight any possible adverse effects and intervene early to help stop any long-term complications. To encourage adherence by allowing regular contact with a member of the healthcare team so any questions/queries can be identified and answered early.

**Case finding**
Patients will be picked up according to the drug treatments prescribed from hospital letters; monthly drug searches will identify any new patients on the listed drugs that have not been otherwise added to the register.

**First consultation**
Initiation and initial monitoring is done by the hospital specialist. Once the condition is clinically stable, the consultant will seek permission to undertake shared care with the GP. The patient will be on a maintenance dose of the drug and they will be reviewed according to the frequency advised in the Hospitals Trust Shared Care Monitoring Protocol for Patients on Disease Modifying Drugs, or SPC/BNF for lithium, amiodarone and mesalazine. The drug is added to the repeat prescription list.

**Review frequency and nature of review**
Review frequency depending on the drug and on the stability of blood test results, according to the Shared Care Monitoring Protocol. Tests will include blood tests for full blood count (FBC), kidney function (U&E) and liver function tests (LFTs); urine tests and blood pressure checks will also be performed, as advised by the Shared Care Protocol. The lead GP/member of DMARD group will confirm which tests need to be done and the frequency and ensure it is clear on the front screen of the patient record.

**Management plan**
The patient attends an appointment with the phlebotomist or practice nurse:
- Blood samples are taken as per the agreed protocol and the results flagged to go to the ‘DMARD group’. A urine test or blood pressure check will also be done where required.
- Another blood test appointment is booked as per local guidance.
- An electronic recall is set for the blood test appointment date.
- A check is made that there is an up-to-date mobile phone and home contact number on the patient record.
- The patient is reminded that they need to ring up for the results for their ‘patient-held record’.

The lead GP/member of the DMARD group will:
- Review each result flagged for the ‘DMARD group’ and write comments on the system for patients to be told their results.
- Confirm exactly which tests should be done and how frequently for new patients identified from hospital letters or the monthly search and detail on the patient record front screen.
- Confirm when patients are no longer taking a drug needing regular monitoring and to take the screen reminder off.
- Liaise with the phlebotomist/practice nurse regarding any queries relating to the regular blood monitoring for these patients.

**Follow-up**
1. A monthly audit of recall dates is performed to check if a blood test has been missed. Where a missed test is found the patient will be contacted by phone call or letter inviting them to make an appointment. Where the patient still does not attend or repeatedly is late for monitoring, the lead GP, or a member of the DMARD group, must be informed.
2. A monthly audit of all patients with DMARDs and other drugs on the protocol is performed to check for any patients started or stopped on these drugs that have not been put on the monitoring system.

**Patients who continue to be monitored by the hospital**
Where monitoring is continued to be done by the hospital:
- The phlebotomist or practice nurse should check with the hospital (department or pathology) that monitoring has been done regularly and that the results are within the normal range.
- A note should be added to the patient record front screen with the date of the last check.

**Involving patients in their care**
Regular contact with a member of the healthcare team allows opportunity for discussions regarding any worries or questions about the drugs and the reasons for monitoring. Patients will be asked to make follow-up appointments for further monitoring to ensure their blood and urine tests are stable and not deteriorating. They will also be asked to ring up for results so that they can record them in their patient-held record. If further communication is required from secondary care, this can be accessed via the Rheumatology helpline number or direct discussion with the appropriate consultant.

Information on support groups can given to patients and carers, for example inflammatory bowel disease nurses, rheumatology nurses.

*Table 3. An example protocol for planned blood test monitoring of patients on DMARDs, lithium, amiodarone and mesalazine using SystmOne*
the patient record front screen with the
date of the last check.

**Extending the scheme**
Other drugs requiring regular monitoring
can be added to the scheme, for example
those detailed in Table 2.

**Audit**
The procedure needs to include regular
audit to ensure that the system is captur-
ing all patients and that they are all hav-
ing timely monitoring.

**References**

**Declaration of interests**
Mrs Wood has received an honorarium from Bayer Healthcare.

Su Wood is a practice pharmacist and independent prescriber, Prescribing Support Services, Shipley, West Yorks.