[1] Department of Clinical Biochemistry, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

[2] School of Medicine, Keele University, Stoke-on-Trent, UK

[3] Department of Gastroenterology, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

Correspondence to CJ Duff
chris.duff@uhnm.nhs.uk

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PRACTICE POINTER

Blood test monitoring of immunomodulatory therapy in inflammatory disease

Nathaniel J Spencer, [1] Anthony A Fryer, [1,2] Adam D Farmer, [2,3] Christopher J Duff[1,2]

What you need to know

- Patients taking immunomodulatory therapy require regular blood test monitoring to identify adverse drug reactions such as hepatotoxicity and bone marrow suppression
- Monitoring levels vary considerably, with under-monitoring and over-monitoring being common
- Multiple guidelines exist, with some variation in recommended practice, although recommendations tend to be based on expert consensus

Immunomodulation is the cornerstone of treatment in many immune mediated inflammatory disorders, including inflammatory bowel disease, autoimmune rheumatic disease, and inflammatory skin diseases. Most require pre-treatment screening blood tests and regular blood test monitoring thereafter to detect potential toxicity. This article seeks to provide a simplified overview of blood test monitoring requirements, and is aimed at general practitioners who, increasingly, are taking responsibility for monitoring and prescribing these medications.

What patients say

Patients may have concerns about taking an immunomodulatory medication. We held a focus group with eight patients who were taking immunomodulatory therapy (three with Crohn's disease and five with ulcerative colitis), who told us:

- They are often concerned about too much suppression of the immune system, especially when risks of infection are discussed
- They often find it difficult to attend for regular monitoring blood tests as services for people of working age are not always available, and systems of testing can be frustrating
- They often do not feel in control of their blood monitoring as feedback from blood tests can be intermittent

What conditions are commonly monitored in general practice?

General practitioners care for a wide range of patients who are treated with immunomodulators. Commonly prescribed immunomodulators are listed in box 1. The conditions treated include psoriasis (UK prevalence 2.2-2.8%[2]), rheumatoid arthritis (UK prevalence 1%[3]), and inflammatory bowel disease (worldwide prevalence 0.3%[4]). In the UK, prescribing responsibilities are transferred from specialist care to primary care using Effective Shared Care Agreements, written local agreements between specialist services and GPs. A large proportion of GPs are either directly involved in caring for patients on immunomodulators or come into contact with them on a regular basis and should therefore be aware of the drug toxicities and monitoring recommendations.

Box 1: Immunomodulators commonly prescribed in inflammatory disease

Initiated in secondary care with ongoing monitoring, and prescribing commonly transferred to general practice

- Sulfasalazine
- Methotrexate
- Thiopurines (including azathioprine, 6-mercaptopurine)
- Leflunomide
- Hydroxychloroquine (no routine laboratory monitoring is required)[1]

Generally monitored in secondary care

- Ciclosporin, mycophenolate mofetil, tacrolimus
- Biological/monoclonal antibody agents, including tumour necrosis factor-alpha inhibitors, T-cell activation inhibitors, interleukin inhibitors, Janus-associated tyrosine kinase inhibitors, and B-lymphocyte associated monoclonal antibodies

Why is monitoring important?

Immunomodulators can cause significant adverse events, including hepatotoxicity, leucopenia, and neutropenia. The prevalence of mild and/or transient blood test abnormalities is relatively common. For example, in a large cohort study of 10 863 patients with rheumatoid arthritis or psoriatic arthritis taking disease-modifying anti-rheumatic drugs, liver enzymes above the reference range occurred in 14-22% of cases, depending on the drug combination; while severe reactions (>2× upper limit of normal) occurred in 1-2% of cases.[5] In a meta-analysis of 66 studies comprising 8302 patients with inflammatory bowel disease on 6-mercaptopurine/azathioprine, the cumulative incidence of myelotoxicity was 7%. The cumulative incidence of severe myelotoxicity was 1.1%.[6] Mortality rates among patients with inflammatory bowel disease who developed myelotoxicity were low at 0.94%.[6] While mild blood test abnormalities are frequent, they are generally transient and even cases with severe blood test abnormalities resolve promptly with discontinuation or dose reduction.[7] Serial abnormal tests are more likely to be associated with pathological liver/bone marrow disease, but risk of progression to serious disease is difficult to assess given that drug exposure is stopped or reduced in most cases.[7] Furthermore,

some uncertainty exists around the degree of risk for liver toxicity attributable to methotrexate treatment, independent to that of other risk factors and pre-existing liver pathology.[7] However, guidelines from the British Society for Rheumatology for methotrexate provide evidence showing, for example, that abnormal liver enzymes are predictive of histological findings on liver biopsy.[1] Monitoring needs to balance detection of abnormalities that may lead to harm against those commonly seen abnormalities that are mild or transient and potentially lead to over-investigation.

How is immunomodulatory therapy initiated in secondary care?

Several baseline screening tests should be undertaken before starting treatment, to assess the risks of serious side effects associated with the particular drug.[1 8-15] These tests (eg, for pregnancy and occult infection) are generally arranged by specialists. Patients may be directed to their GP to ensure that relevant vaccinations are up to date. Some agents, such as leflunomide and methotrexate, are contraindicated in pregnancy.

Monitoring for adverse effects immediately after starting treatment, or after a dose change, is generally the responsibility of specialists. These blood tests largely reflect those used for longer-term monitoring, but with increased frequency (every 1-2 weeks) until stable dosing is achieved (usually within 1-3 months[13]). Further details can be found in specialist guidance.[1 8-15]

Regular, long term monitoring (ie, for the duration of treatment with the drug while on a stable dose) is often performed in general practice, although in some cases this may remain the responsibility of specialists. Effective and explicit handover of care from specialists to general practitioners is critical and needs to be understood by all parties, including the patient. In the UK, this should be done via an Effective Shared Care Agreement, which should clearly detail which tests are required, who is responsible for testing, how often, and what action is needed in the event of abnormalities. Furthermore, at an individual patient level, communication from specialist outpatient clinics should include a statement regarding the ongoing monitoring requirements.

What do guidelines say about monitoring requirements for long term treatment?

Guidance on which blood tests to perform and the frequency of testing is provided by the relevant professional bodies, the National Institute for Health and Care Excellence (NICE) and the British National Formulary (BNF)[1 8-15] and is summarised in the infographic. These guidelines are generally in agreement in terms of which tests to undertake and the frequency of monitoring: 8-12 weekly for full blood counts and liver function tests to identify any bone marrow or hepatic toxicity, and renal function tests to assess capacity for drug clearance (eg, for renally excreted drugs such as 6-mercaptopurine/azathioprine, which can exacerbate risk of toxicity) and/or nephrotoxicity itself (eg, for drugs such as methotrexate). The exception is the American College of Gastroenterology guidelines[15] which do not recommend an explicit frequency for blood testing, stating only that tests should be done "regularly."

In specific cases, additional tests are recommended. For example, in patients with psoriasis on methotrexate, measurement of procollagen III N-terminal peptide is also advised as an indicator of hepatic fibrosis, although this is usually performed in secondary care.[9] Monitoring requirements are tailored to individual risks, and the recommendations described here and in the infographic are provided only as a guide. Some patients, such as those with relevant comorbidities (eg, malignancy) or on multi-agent therapy (eg, combination therapy as is commonly used in rheumatoid arthritis) may be at higher risk of adverse events and therefore warrant closer monitoring.[1]

What do guidelines recommend for managing abnormal results?

Variations exist between guidelines on drugs and conditions in the UK[1 8-13] and elsewhere,[14 15] particularly in the action limits (ie, blood test values outside which clinical action is warranted) used, although the principles remain the same (supplementary file).

6-mercaptopurine/azathioprine

For 6-mercaptopurine/azathioprine, the British Society for Rheumatology guidelines suggest monitoring a wider range of parameters, including eosinophils, platelets, mean corpuscular volume, and albumin,[1] which are not mentioned in other guidelines. Slight variations in action limits are also evident for neutrophils, transaminases, and assessment of renal function. While in each case guidelines suggest contacting respective specialists, the wording varies in intensity. For instance, the British Society for Rheumatology guidelines state for abnormal transaminases: "Contact rheumatology team urgently and consider interruption in treatment,"[1] while the British Society of Gastroenterology uses the phrase "Stop and check thiopurine metabolites" (a test requested by specialists).[10] The British Association of Dermatologists recommendations imply a more pragmatic approach to abnormal results based on more "careful evaluation and increased frequency of repeat testing," although it does acknowledge that "dose reduction or drug withdrawal may be needed."

Methotrexate

For methotrexate, the British Society for Rheumatology guidelines are the same as for 6-mercaptopurine/azathioprine.[1] By contrast, the British Association of Dermatologists does not include eosinophils or albumin in its recommendations for monitoring methotrexate, and in cases of abnormal results, suggests discussion with haematology or gastroenterology in cases of suspected myelo or hepatotoxicity, respectively.[9] The British Society of Gastroenterology guidelines for methotrexate require monitoring for a more limited range of parameters (white cell count and transaminases only) and suggest stopping treatment if these are outside action limits.[10]

Leflunomide and sulfasalazine

Recommendations on handling abnormal results for patients on leflunomide and sulfasalazine are only provided in the British Society for Rheumatology guidelines and mirror those used for patients taking 6-mercaptopurine/azathioprine and methotrexate.[10]

In all cases, results of laboratory tests should be interpreted in the context of the individual patient, the severity, the speed of change of any abnormalities, and the expected action of the therapeutic agent. For example, a sudden change in liver function test results in an ostensibly asymptomatic patient who has otherwise tolerated a drug well may reflect other causes of liver damage. In this context, awareness of local pathways for managing patients with abnormal test results is important.

Practical challenges

Growing evidence suggests that the number of patients who are under and over-tested when compared with guidance is considerable and highly variable across a range of conditions.[16-18] Reasons for this are complex and multifactorial, but include patient, practitioner,

and system factors (table 1).[16 17] Included in this is the frequent need for interaction between primary and secondary care, and the availability of specialist advice. The implications of under and over-testing are significant. For instance, under-testing risks adverse events such as liver damage or bone marrow suppression, while over-testing is costly to the NHS, increases the workload of over-stretched primary care services, and risks false positives and over-diagnosis. In addition, frequent testing is inconvenient for patients (eg, time off work, discomfort, costs),[17 18] potentially having a negative effect on the acceptability of their treatment plan. Testing strategies therefore need to balance safety, cost, deliverability, and the burden of monitoring for patients.

Table 1 | Tips for improving monitoring

Factor	Improvement options
Patient	1. Convenience: Could phlebotomy services be provided outside normal working hours or in a more convenient location? 2. Education and motivation: Does the patient understand the need for the test? Could patient information emphasise this? 3. Engagement: How can test results best be provided and explained to patients?
Clinician	1. Responsibility: Is it clear who is responsible for organising the testing? Are the methods used to hand over this responsibility between specialist and general practice effective? 2. Education: Are the key healthcare professionals aware of the need and importance of testing? 3. Motivation: Are clinicians clear on the benefits of monitoring? What are the incentives?
System	1. Infrastructure: Is there a system for identifying patients who need testing and when the next test is due? 2. Test requesting: Are there more user-friendly ways of requesting appropriate tests, such as by using standardised test panels for specific drugs via electronic test requesting systems. 3. Results visibility: Are primary and secondary care staff able to view results requested by the other? 4. Engagement: Are laboratory staff engaged in providing support (technical, logistic and educational)?

Improvements in monitoring will need to address the evidence underpinning the frequency of testing and ensure that healthcare infrastructure is in place, such as by use of electronic reminder systems.[19 20] Critically, approaches to reduce under and over-testing will need to engage patients, such as by making sample collection more convenient and enabling patients to be more involved in managing their condition by providing access to test results and/or educational advice on the importance of testing.[17 21] Given their existing involvement in blood testing for specialists and general practitioners, clinical laboratories may be uniquely placed to oversee this monitoring service.

Uncertainties

The guidance on monitoring for many of the common agents is clear and broadly similar; however, high quality evidence on which to base these recommendations is lacking, and recommendations are frequently based on expert opinion. For example, the level of evidence for recommendations on acting on abnormal test results for patients on methotrexate in the 2016 British Association of Dermatologists' guidelines on psoriasis[9] was identified as 2+ (based on well conducted case-control or cohort studies). British Society of Gastroenterology recommendations for blood test monitoring 6-mercaptopurine, azathioprine, or methotrexate in patients with inflammatory bowel disease were graded as based on "low-quality evidence," and the British Society for Rheumatology guidelines for monitoring disease modifying anti-rheumatic drugs (DMARDs) were graded as 2B (weak recommendations based on moderate evidence).[1] The authors of a systematic review of thiopurine-induced liver injury in patients with inflammatory bowel disease concluded: "Despite a lack of evidence that monitoring of liver tests is necessary in patients receiving 6-mercaptopurine/azathioprine, routinely performed laboratory controls including liver tests seem recommendable."[22] The need for additional evidence is highlighted by a recent call from the UK National Institute for Health Research Health Technology Assessment funding stream for studies to provide evidence on testing frequency specifically for patients with common inflammatory diseases. This includes the need to assess patient views on what is often relatively frequent and potentially inconvenient testing.

Impact of covid-19

In the context of covid-19, some variations exist on guidance for blood test monitoring in established immunomodulatory therapy:

- The British Society of Gastroenterology advises reducing any therapy-associated monitoring blood tests to minimum safe frequency, and suggests that many routine tests can be deferred until the situation has improved, depending on local capacity[23]
- The British Association of Dermatologists advises that patients who have been on the same medication for a substantial period of time with adequate disease control and blood monitoring that has remained satisfactory may be able safely to increase the time interval for blood monitoring on a case-by-case basis[24]
- The British Society for Rheumatology advises that clinicians may need to be flexible about blood testing and that it is usually safe to reduce blood testing frequency to three-monthly or even less in stable patients. It states that cases need to be reviewed on an individual basis, weighing up the risks of continuing without blood testing, compared with the benefit of staying on DMARDS[25]
- Guidance for monitoring during initiation remains unchanged.
- NICE recommends that patients follow comprehensive social distancing and hand hygiene measures for 14 days before having planned care; this includes diagnostic tests.[26]
- For individuals with symptoms associated with covid-19, the British Society for Rheumatology guidance also suggests:[25]
  - considering stopping medication and seeking specialist advice on when to restart
  - undertaking additional blood tests after self-isolation and within two weeks of restarting medication
  - if these tests are within the normal range, reverting to a flexible monitoring schedule on a case-by-case basis (see above); if abnormal, seek specialist advice

Education in to practice

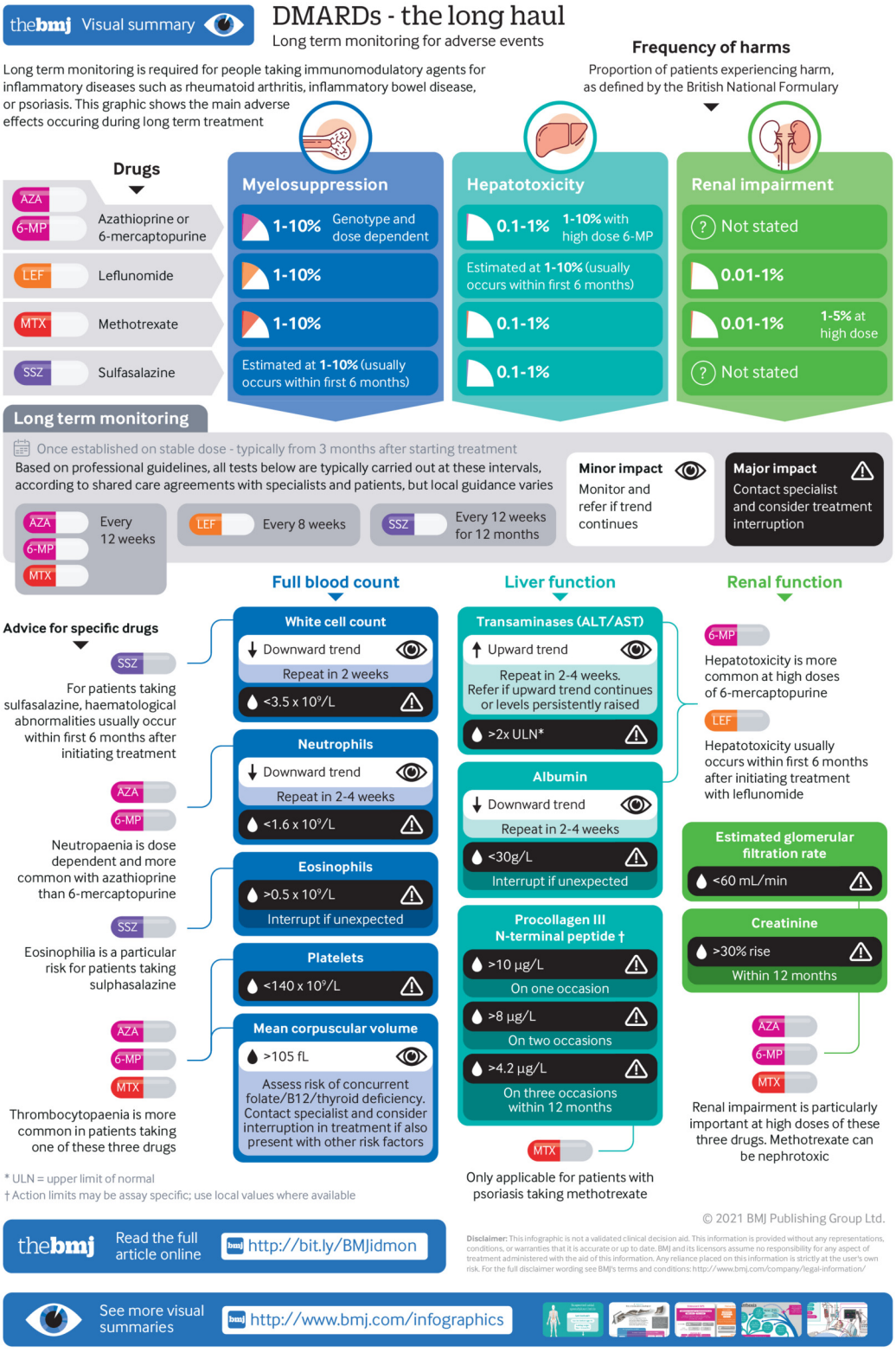
- What impact does immunomodulatory treatment and monitoring have on your patients' quality of life?
- What systems do you have in place to ensure adequate monitoring?
- How well does your patients' blood test monitoring conform to guidelines? Consider auditing attendance for blood tests, frequency of abnormalities, and patient recall for abnormalities

How this article was made

We reviewed the British National Formulary, current guidelines from the National Institute for Health and Care Excellence and major professional bodies including the American Academy of Dermatology, American Society of Gastroenterology, American College of Rheumatology, British Association of Dermatologists, British Society for Rheumatology, British Society for Paediatric and Adolescent Rheumatology, British Society of Gastroenterology, British Society of Paediatric Gastroenterology, Hepatology and Nutrition, European Crohn's and Colitis Organisation, and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. We reviewed UK national Effective Shared Care Agreements. We searched the Cochrane database and Medline using the search terms "Guidelines," "DMARD(s)," "Immunomodulators," "Monitoring," "Blood Test Monitoring," "Thiopurine," "Azathioprine," "Methotrexate," "Leflunomide," "Sulfasalazine," "Hydroxychloroquine & Adverse events."

How patients were involved in the creation of this article

We held a focus group with eight patients who are receiving immunomodulatory treatment and asked them about the impact of their treatment on their daily lives. Their responses informed the "What the patients say" box and the focus throughout the article on the impact of monitoring on patients.



I have read and understood *The BMJ* policy on declaration of interests and declare the following interests: none.

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