RHEUMATOLOGY

Guidelines

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BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs

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GUIDELINES

Introduction

Successful treatment of inflammatory rheumatic disease involves the use of DMARDs to suppress the disease process. In recent years, treatment paradigms have shifted, with more emphasis on early diagnosis and more intensive treatment strategies, often using DMARDs in combinations, with the aim of achieving disease remission [1–3]. This approach has been shown to give better disease outcomes, especially when instituted early on in the disease course.

Many of the treatments used have potential for harm as well as benefit. Appropriate screening prior to DMARD initiation, as well as vigilant monitoring during therapy, are required to minimize risks. This current guideline supersedes the previous 2008 BSR/BHPR guideline [4].

Purpose and scope

Background and need for guidance

The previous BSR guidelines published in 2008 required revision because the treatment paradigms have evolved and the evidence available to base decisions upon has broadened

NICE has accredited the process used by the BSR to produce its guidance for the use of non-biologic DMARDs. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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[4]. The 2008 Guideline Working Group (GWG) lead and a new GWG confirmed a need for an updated guideline.

Objectives of this guideline

The purpose of this guideline is to provide up-to-date, evidence-based recommendations for the safe use of non-biologic DMARDs in adults (>16 years old). The guideline is aimed at practitioners in both primary and secondary care settings. Specific areas that have been focused upon in this guideline include the following: recommendations regarding baseline screening prior to DMARD initiation; implications of co-morbid illness for DMARD prescribing; recommendations regarding monitoring for toxicity; management of DMARDs during intercurrent illness or surgery; and shared care guidelines.

DMARDs covered by this guideline

The following DMARDs are covered in this guideline: apremilast (APL), AZA, CSA, HCQ, LEF, mepacrine, MTX, minocycline (MCN), MMF, sodium aurothiomalate/myocrisin (gold), SSZ and tacrolimus (TCL).

It is expected that this guideline should be viewed along with individual drug summaries of product characteristics (SPCs) that are freely available online at the medicines compendium [5]. It is always the responsibility of the treating clinician to consider the individual risks and benefits with any patient and ensure that the patient is involved in making an informed choice about treatment.

The areas the guideline does not cover

The guideline does not cover the indications for DMARD therapy. There are disease-specific recommendations published both nationally and internationally, as well as guidance from National Institute for Health and Care Excellence (NICE) that address treatment indications. The guideline does not cover the use of biologic therapy or other selective non-biologic DMARDs (e.g. kinase inhibitors). Biologic prescribing is reviewed in a separate BSR/BHPR guideline [6]. The guideline does not cover prescribing in relation to pregnancy or breast-feeding, which are reviewed in separate BSR/BHPR guidelines [7, 8]. The guideline does not cover prescribing for patients <16 years of age. Monitoring guidance for penicillamine is no longer included in this document because this drug has disappeared from routine use as a DMARD in contemporary practice [9]. The guideline does not cover drug interactions between DMARDs and non-rheumatological drugs.

Target audience

The primary audience consists of health professionals in the UK directly involved in managing patients with rheumatic disease. This audience includes rheumatologists, rheumatology nurses and allied health professionals, specialist pharmacists, rheumatology speciality trainees, pharmacists, general practitioners (GPs), practice nurses and the patients themselves. The guideline will also be useful to physicians in other specialities and to surgeons who manage patients with rheumatic disease.

Stakeholder involvement

The BSR Standards, Guidelines and Audit Working Group commissioned the guideline update with Dr James Galloway as the new GWG Chair. A GWG consisting of representatives from relevant stakeholders (see Table 1 for full list) was convened, and all members of the GWG made declarations of interest in line with BSR Policy.

Involvement and affiliations of stakeholder groups

The GWG consisted of rheumatologists from a range of clinical backgrounds, pharmacists, rheumatology specialist nurses, general practice and a patient. All members of the GWG contributed to the process for agreeing key questions, guideline content, recommendations and strength of agreement. Declarations of interest from all GWG members are publically available on the BSR website.

Rigour of development

This guideline has been developed in line with the BSR's Guidelines Protocol. It is important to acknowledge that there are no trials comparing different strategies for DMARD screening and monitoring. However, there are numerous studies that have reported on the risk factors for and the incidence of adverse events with DMARD therapy. In addition, there are numerous national and international guidelines already in existence. Therefore, the following approach was taken for each DMARD: review of the current SPC for the drug with respect to baseline screening and subsequent monitoring; evaluation of the rate of specific toxicities for each agent; and review of published guidelines from other national and international societies for each drug.

The current SPC for each drug was accessed online at [5] using SPC documentation current to September 2015. Where more than one SPC was available for a drug (in the case of multiple manufacturers), all SPCs were reviewed.

Evaluation of toxicity as well as review of published guidelines involved a systematic search of the literature. Common search strategies were used, searching for placebo-controlled trials of the named DMARD in relevant rheumatic disease indications. Original articles accessible in the English language containing data pertaining to adverse event rates were used. If adverse event rates were not available in the published literature (including supplementary materials), authors were contacted to request further information. Searches were conducted using MEDLINE, Cochrane, PUBMED and EMBASE. A manual search from the references cited by generated articles was also conducted. The literature searches for the individual drugs took place between April and September 2015.

Grading of the evidence

This guideline was developed in line with BSR's Guidelines Protocol using Royal College of Physicians (RCP), Scottish Intercollegiate Guidelines Network (SIGN) and AGREE II methodology to determine level of evidence and strength of evidence. A core panel within

Table 1 List of members of the Guideline Working Group

Name	Role	Affiliation
James Galloway	Chair DMARD GWG	King's College London
Jo Ledingham	Consultant Rheumatologist and Chair BSR SAGWG	Portsmouth NHS Hospitals Trust
Rachel Gorodkin	Consultant Rheumatologist	Central Manchester University Hospitals NHS Foundation Trust
Nicola Gullick	Consultant Rheumatologist	King's College Hospital NHS Foundation Trust
Katherine Irving	Consultant Rheumatologist	King's College Hospital NHS Foundation Trust
Sander van Leuven	Consultant Rheumatologist	Radbound University Medical Centre, The Netherlands
Andrew Jeffries	Consultant Rheumatologist	Blackpool Teaching Hospitals NHS Foundation Trust
Patrick Gordon	Consultant Rheumatologist	King's College Hospital NHS Foundation Trust
Dimitrios Christidis	Speciality Trainee Rheumatology	Epsom and St Helier University Hospitals NHS Trust
Sarah Galloway	General Practitioner	South Brent Health Centre, Devon
Eranga Hayes	General Practitioner	North Street Medical Practice, Peterborough
Scott Mercer	Pharmacist	Guy's and St Thomas' Hospital NHS Foundation Trust
Melissa Aris	Rheumatology nurse specialist	Central Manchester University Hospitals NHS Foundation Trust
Janice Mooney	Senior Lecturer and Nurse Practitioner	University of East Anglia
Jean Burke	Patient Representative	National Rheumatoid Arthritis Society

GWG: guideline working group; NHS: National Health Service; SAGWG: Standards, Audit and Guidelines Working Group.

the GWG convened on four occasions to review evidence, resolve disagreements and determine recommendations. A draft document was then circulated to the full GWG for review. Each suggested recommendation in the final document was evaluated by all members and subjected to a vote relating to strength of agreement on a scale of 1 (no agreement) to 10 (complete agreement). The strength of agreement from across the GWG is presented for each recommendation as a percentage (e.g. 100% would imply all responses were 10/10).

The recommendation statements are presented at the beginning of each section, which includes the relevant references selected from our systematic search. Accompanying each recommendation statement in parenthesis is a statement reflecting the strength of recommendation and also quality of supporting evidence.

The GRADE approach to assessing the quality and strength of recommendations was adopted [10]. Various adaptions of the GRADE process have been used. This guideline has adopted the following standard.

Strength of the recommendation

A recommendation is a strong recommendation to do (or not do) something where the benefits clearly outweigh the risks (or vice versa) for nearly all patients. This guideline uses the number 1 to reflect a strong recommendation. A weak recommendation is made either when risks and benefits are more closely balanced or are more uncertain. This guideline uses a number 2 to reflect a weak recommendation.

Quality of evidence

Assessment of evidence quality in GRADE reflects confidence in the estimates of benefits, harms and burdens. This guideline uses three levels and uses a letter (A, B or C) for high, moderate or low/very low quality of evidence.

High quality

Further research is very unlikely to change our confidence in the estimate of effect. High-quality evidence typically comes from well-performed randomized controlled trials (RCTs) or other overwhelming evidence (such as well-executed observational studies with very large effects).

Moderate quality

Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Moderate-quality evidence typically comes from randomized trials with important limitations, or from other study designs with special strength.

Low quality

Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Low-quality evidence typically comes from observational studies or from controlled trials with very serious limitations. Very low-quality evidence typically comes from non-systematic observations, biologic reasoning or observational studies with serious limitations.

Limitations of the guideline

The literature search was limited to articles accessible in English language and available through standard University library channels. It is notable that a small body of evidence is excluded by limiting to English language, especially pertaining to Japanese patients. This is relevant as Japanese patients may have different adverse event profiles (e.g. differences in routes of metabolism for

drugs such as MTX [11]) and more intensive monitoring strategies may be appropriate.

Plan for review

The planned review date for this guideline will be 2019. However, important interim changes will be updated on the BSR website.

Guideline

Each of the seven sections of the guideline (commencing DMARDs, drug-specific recommendations, co-morbidities, monitoring, interrupting therapy, shared care agreements and response to laboratory abnormalities) will now be discussed in detail. For each statement, a review of the evidence will be presented followed by the guideline recommendation.

Commencing DMARDs

Generic recommendations before commencing any DMARD

(i) The decision to initiate DMARDs should be made in conjunction with the patient/carer and be supervised by an expert in the management of rheumatic diseases (GRADE 1B, 100%).
(ii) Patients should be provided with education about their treatment to promote self-management (GRADE 1B, 100%).
(iii) When appropriate, patients should be advised about the impact of DMARD therapy upon fertility, pregnancy and breastfeeding (GRADE 1B, 100%).
(iv) Baseline assessment should include height, weight, blood pressure and laboratory evaluation [full blood count (FBC), calculated glomerular filtration rate (GFR), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), albumin] (GRADE 1C, 97%).
(v) Patients should be assessed for co-morbidities as these may influence DMARD choice, including evaluation for respiratory disease and screening for occult viral infection (GRADE 1C, 97%).
(vi) Vaccinations against pneumococcus and influenza are recommended (GRADE 1C, 97%).

Evidence supporting recommendations

Recommendation: initation of DMARDs

Observational studies have demonstrated superiority of care for patients with inflammatory arthritis supervised by rheumatologists [12–16]. Patients with RA cared for by non-rheumatologists are more likely to have delays in commencing therapy, are less likely to achieve disease remission and have more radiographic progression [17]. Although data are lacking for other rheumatic diseases, it seems wise to extend this recommendation to all rheumatic diseases requiring DMARD therapy. In the setting of the National Health Service (NHS), a rheumatologist is defined as a doctor with specialist accreditation in rheumatology.

The evidence underpinning the recommendation for shared decision-making will not be reviewed here. Patient involvement in decision-making is a core tenet of contemporary medical care. A comprehensive review of the available evidence is available online, with summary evidence presented from almost 800 reviews on the topic [18].

Recommendation: patient education

Substantial research has been done evaluating the benefit of patient education in RA, including a Cochrane review in 2002 [19]. The Cochrane review concluded that education had a positive effect in terms of both patient-reported outcome and objective measures of clinical response. However, the benefits observed were not observed over a longer duration of follow-up. A more recent review from 2011 has extended the evidence base, demonstrating efficacy of group education as well as one-to-one delivery [20]. Education is recommended as a core component of care by the NICE quality standards guideline for RA [21].

Recommendation: pregnancy and breastfeeding

There are separate BSR guidelines relating to DMARD use for people planning pregnancy [7, 8]. Therefore, beyond the recommendation that the issue be considered for discussion in relevant patients, this guideline will not cover the subject in more detail so as to avoid duplication of recommendations.

Recommendation: baseline assessment

There are established associations between inflammatory autoimmune disease and cardiovascular risk (including hypertension) [22]. There is a rising prevalence of obesity in the UK [23]. Body mass and blood pressure both have direct relevance to DMARD prescribing. AZA and HCQ are prescribed on a weight-based regimen, and LEF, TCL and CSA all require assessment of blood pressure. Therefore, although there may be organizational barriers to height and weight measurement in some outpatient settings, the consensus group agreed that best practice should include documentation of height, weight and blood pressure prior to commencing any DMARD therapy for all patients.

It may be of value to obtain an ECG in some patients, especially when commencing medications associated with hypertension. The SPC for TCL specifically recommends baseline ECG when prescribed in the context of transplantation medicine.

In addition to baseline clinical assessment, a number of laboratory tests are important as part of the patient evaluation prior to commencing DMARD therapy. Baseline tests serve two functions in DMARD assessment: they act as a screening tool for occult disease (renal or hepatic dysfunction); and they provide a reference point for future comparison. Considering the former component, case-finding of occult disease, the evidence would suggest that in otherwise healthy individuals, the pick-up rate of

routine investigations is low (FBC 0.9%, chemistry panel 2.8%) [24]. In a population with rheumatic disease requiring DMARD therapy, it is likely that the incidence of significant abnormalities will be higher than in a healthy population. For example, in established RA it is apparent that the overall burden of co-morbidity is high [25].

Combining the need to identify baseline abnormalities with the advantage of having a pre-treatment measurement to look back upon, baseline laboratory evaluation is an important component of DMARD screening. Therefore, and in line with the current NICE guideline, it is highly recommended to assess the following baseline laboratory parameters: FBC, renal and liver profile [21].

A variety of blood tests are available that are often referred to within a liver profile. The most common tests used in clinical practice include the serum aminotransferases, bilirubin, alkaline phosphatase, albumin and clotting time. These can be divided into tests that assess liver cellular injury (e.g. aminotransferases) and tests that reflect synthetic liver function (albumin and clotting). It is recommended that at least one test of each aspect is included in assessment of the liver.

The serum aminotransferases (formerly called transaminases) are sensitive indicators of drug-induced liver cell injury [26]. The most commonly measured are ALT (serum glutamic–pyruvic transaminase) and AST (serum glutamic–oxaloacetic transaminase). There was no robust evidence to support either ALT or AST preferentially, and it is likely that the choice of test will depend upon local availability of assays.

Laboratory evaluation of patients with rheumatic disease frequently includes measurement of markers of inflammation (ESR, CRP). These tests are part of the assessment of the underlying rheumatic disease rather than a requirement for monitoring of DMARD therapy. It may, of course, be appropriate for local services to combine blood tests for disease monitoring with DMARD monitoring.

Recommendation: evaluation for co-morbidity

Multi-morbidity is common in contemporary clinical practice, affecting >20% of the general population [27]. Co-morbid conditions have significant implications for DMARD prescribing and therefore awareness of co-morbid conditions at baseline is highly relevant. It is beyond the scope of this guideline to review all co-morbidities. Attention will be paid to the most prevalent co-morbidities and those of particular relevance to DMARD prescribing.

The initial baseline clinical and laboratory evaluation will help to identify cardiovascular, liver and renal co-morbidity. Specific evaluation for lung disease and occult infection are discussed here.

Screening for lung disease prior to DMARD therapy

Respiratory diseases can arise as a direct complication of rheumatic disease. The lifetime risk of interstitial lung disease (ILD) in RA is ~10%, and this risk is substantially greater in some CTDs [28–30]. In addition to lung disease related to the rheumatic disease, chronic obstructive pulmonary disease (COPD) is also prevalent in the UK. Data from The Health Improvement Network primary care database including subjects aged between 35 and 89 years (n = 2 839 694) revealed a prevalence of 3% [31]. Acknowledging that smoking is a shared risk factor for both COPD and rheumatic diseases (most notably RA), assessment for lung disease is relevant to rheumatology care irrespective of DMARD therapy.

Chronic lung disease is an important consideration when initiating DMARD therapy, as a number of DMARDs have been associated with acute pneumonitis. In a patient with reduced respiratory reserve, a sudden deterioration in respiratory function could have devastating consequence. Therefore, evaluation for chronic lung disease prior to initiation of DMARD therapy is indicated.

In all patients, this should include a history of respiratory symptoms and respiratory examination. In patients with a clinical suspicion of parenchymal lung disease, formal lung function testing and appropriate imaging (chest radiograph with or without high-resolution CT imaging) should be performed and referral to a respiratory specialist be considered. Any patient currently smoking should be offered access to smoking cessation services.

This guidance differs from previous recommendations with respect to lung disease. Screening for lung disease should be undertaken at clinician discretion on a case-by-case basis. The extent of screening should be influenced more by a patient's clinical features and risk factors for lung disease (e.g. underlying autoimmune disease or smoking history) rather than subsequent DMARD choice.

Screening for occult viral infection prior to DMARD initiation

Hepatitis B and C are blood-borne infections of the liver. The viruses can result in chronic infection that is associated with an increased risk of chronic liver disease and hepatocellular carcinoma [32]. It is important to recognize that an estimated 90% of people infected with hepatitis B or C are unaware of their status [33].

NICE currently recommends that all people who are at increased risk of hepatitis B infection are offered testing and vaccination [34]. Examples of people at increased risk of hepatitis B infection compared with the general UK population who may be seen in adult rheumatology services include people born or brought up in a country with an intermediate or high prevalence (⩾2%) of chronic hepatitis B. This includes the following: all countries in Africa, Asia, the Caribbean, Central and South America, Eastern and Southern Europe, the Middle East and the Pacific islands; people who have ever injected drugs; men who have sex with men; people who may have been exposed to sexually acquired infection; and prisoners, including young offenders.

HIV infection, sharing similar risk factors with hepatitis B infection, represents another important consideration when initiating DMARDs. An estimated 107 800 (95% credible interval: 101 600, 115 800) people were living with HIV in the UK in 2013 [35]. The overall prevalence

was 2.8/1000 population aged 15–59 years, with a quarter of people unaware of their status. One in four people living with a diagnosed HIV infection is now aged ⩾50 years.

Relevant to rheumatology practice, hepatitis B can reactivate with DMARD therapy (including even HCQ [36]). There are fewer data with respect to the effect of DMARD therapy and hepatitis C infection, however co-infection with HIV has been shown to be detrimental, suggesting that immunodeficiency may accelerate HCV progression [37, 38]. Prescribing DMARDs to an individual with undiagnosed HIV infection can further increase the risk of infection.

Acknowledging that there are now effective therapies for viral hepatitis and HIV, there is a strong rationale for offering screening to all patients prior to commencing immunosuppression. This recommendation is in line with recommendations from other national and international societies [39–43].

Recommendation: advice on vaccinations

National recommendations regarding vaccination are published and regularly updated by the Joint Committee on Vaccination and Immunization (JCVI) in the form of the Green Book [44]. Chapter 7 of the Green Book deals specifically with patients commencing immunosuppression and should be regarded as the definitive source of information regarding vaccination.

Recommended vaccines for all patients include influenza and pneumococcus. Influenza vaccine should be administered annually. Pneumococcal vaccination should be administered as a single dose of the polysaccharide PPV-23 (Pneumovax). Ideally, the pneumococcal vaccine should be administered prior to the initiation of DMARDs; however, if this is not possible it should be administered irrespective.

Although rheumatologists are responsible for the initiation of immunosuppressive agents, it remains in the domain of primary care to ensure vaccination. Primary care practices are commissioned to vaccinate people >65 years old and those <65 years old at risk (including patients with rheumatic diseases on DMARDs) through the NHS Enhanced Services Payment scheme.

The JCVI recommends that in severely immunocompromised adults, a different schedule using a single dose of the conjugate PCV-13 (Prevenar) followed by PPV-23 at least 2 months later be used. The JCVI provides examples of severe immunocompromise (e.g. bone marrow transplant), none of which includes a rheumatic disease. However, there are clearly settings in which patients with autoimmune disease are subjected to profound immune defects and therefore clinicians need to consider patients on a case-by-case basis. Liaison with immunology specialists may be appropriate.

Clinical teams should educate patients regarding the recommendations for vaccination, as well as directly inform the patient's primary care providers. Several large audits have revealed low uptake of vaccinations amongst patients with rheumatic disease, especially for the pneumococcal vaccination amongst patients below the age of 65 years [45, 46].

Live vaccines are not recommended in patients on immunosuppression. This is relevant for patients seeking vaccination for foreign travel (e.g. yellow fever vaccination) and also the shingles vaccine, which will be discussed further.

A shingles vaccine (Zostavax) is currently recommended by the JCVI for people over the age of 69 years. Zostavax reduces the risk of shingles by ~50% in immunocompetent adults aged 60 years and older [47]. There are limited data on the vaccine efficacy in immunocompromised populations. The vaccine is live and therefore relatively contraindicated in individuals who are immunosuppressed. Low levels of immunosuppression are not considered an absolute contraindication, and the JCVI Green Book addresses this, recommending that low-dose CSs (prednisolone <20 mg daily) and oral DMARD therapy at standard doses are not a contraindication in most patients, although clinician discretion is advised.

There is evidence that people with rheumatic diseases have a higher incidence of shingles than the general population [48]. However, in the absence of robust evidence for efficacy or safety in patients on immunosuppression, to date the JCVI recommendations for Zostavax have not been extended to younger age groups in the rheumatic disease population.

Drug-specific recommendations

(i) MTX: All patients should be co-prescribed folic acid supplementation at a minimal dose of 5 mg once weekly (GRADE 1B, 97%).

(ii) AZA: Patients should have baseline thiopurine methyltransferase (TPMT) status assessed (GRADE 1A, 97%).

(iii) HCQ: Patients should have baseline formal ophthalmic examination [ideally including objective retinal assessment; for example, using optical coherence tomography (OCT)] within 1 year of commencing an antimalarial drug (GRADE 2C, 88%).

Evidence supporting recommendations

Recommendation: MTX

Supplementation of folic acid in RA patients during MTX treatment significantly reduces the risk of abnormal liver biochemistry, gastrointestinal side-effects (e.g. nausea, vomiting and abdominal pain) as well as MTX discontinuation (for any reason) [49]. Prescribing folic acid (minimal dose 5 mg/week) with MTX is strongly recommended.

There was insufficient evidence to make a recommendation regarding which day of the week folic acid should be administered, although the overwhelming majority of clinical trials have avoided folic acid supplementation on the day of the MTX dose.

Recommendation: AZA

AZA is a prodrug that is rapidly converted to 6-mercaptopurine. There are two major metabolic pathways: catabolic oxidation by xanthine oxidase (discovered by the Nobel Laureate Gertrude Elion, who also discovered allopurinol, which inhibits xanthine oxidase and would therefore block the clearance of AZA, hence the reason for exerting extreme caution in co-prescribing AZA and allopurinol); and anabolic metabolism via TPMT. Approximately 0.3% of the population have very low TPMT activity, reflecting inheritance of two low-activity *TPMT* alleles [50, 51]. Patients with very low TPMT activity are unable to clear even low doses of AZA effectively, and exposure can lead to profound and prolonged pancytopenia that may be fatal [52, 53]. A meta-analysis of 67 studies (mostly retrospective) showed that 86% of patients with both alleles develop significant myelosuppression [54]. Myelotoxicity can also be observed in individuals who carry a single low-activity allele exposed to conventional AZA doses [55, 56]. There is evidence to suggest that reduced dose of AZA (25–75 mg daily) can be used in patients with low (but not absent) TPMT activity levels; however, the studies are of relatively small size and none had safety as a primary end point [57, 58].

However, it is important to note that in an IBD study, a majority (73%) of cases of myelosuppression observed with AZA were observed in patients without any of the *TMPT* alleles [59]. For this reason, TMPT screening cannot be considered a substitute for subsequent monitoring.

In 2008, a systematic review appraising the cost-effectiveness of TMPT screening concluded that the process was cost neutral. However, as the cost of TPMT testing is continuing to reduce and cases of severe neutropenia in patients who lacked pre-screening continue to be reported, the argument for TPMT assessment is now strong [60].

TPMT screening may not be available in all laboratory settings, especially in primary care. In some service settings, TPMT screening will be required to be performed in secondary care. In situations where no TPMT testing is available, then it would be reasonable to increase laboratory monitoring frequency to weekly in the initiation phase of treatment.

Recommendation: HCQ

HCQ, prescribed at a dose of 200 mg once or twice daily (based upon ideal weight and not exceeding 6.5 mg/kg) is a frequently used DMARD. Ocular complications with HCQ therapy are rare, but potentially serious. Complications include both corneal and retinal disease. Since the last guideline was published, a number of changes have occurred in the available tools to screen for ocular disease, as well as new evidence regarding the incidence of eye complications.

An important consideration is that there is evidence suggesting that weight-based prescribing frequently fails to consider ideal body weight (rather than actual body weight) and, as a result, patients are exposed to doses higher than 6.5 mg/kg [61]. Exposure to higher doses is associated with an increased risk of ocular toxicity [62].

A registry-based study of 3995 patients with RA or systemic lupus who used HCQ found that the risk of toxicity was low in the first 5–7 years of exposure (0.3%) [63]. The point estimates of risk rose steadily thereafter; risks at 10, 15 and 20 years were 1, 2.1 and 3.1%, respectively. Likewise, risk was significantly greater for patients treated with a cumulative dose of >1000 g of HCQ, compared with those treated with less (odds ratio = 4.5, 95% CI: 1.4, 14.5). A 2014 study using more sensitive measures to detect retinopathy reported an even higher risk [64, 65]. The identified baseline risk factors for ocular complications include older age, renal disease and pre-existing retinal disease [63].

In addition to more robust evidence clarifying the risk of retinal toxicity from anti-malarial therapy, there have also been advances in screening and diagnosis. Historical recommendations relied upon baseline screening with colour charts or Amsler grids, which lack sensitivity and specificity. Objective testing, using techniques such as spectral domain OCT, have been shown to be more sensitive at screening for HCQ retinopathy [66–69]. These revised recommendations are in line with the current guidance in the USA [70].

The aim of the screening is the recognition of a preclinical stage of retinal disease before bull's eye retinopathy develops, which signifies an advanced stage that is irreversible [63, 71, 72]. The risk of ocular toxicity within the first 5 years of treatment is extremely low [73]. In one study of 1207 patients, only one case of HCQ toxicity was confirmed [62]. In the largest study so far, which included 3995 patients, HCQ toxicity increased after 5–7 years with a prevalence of 1% [63]. It is for this reason that the existing recommendation is to undertake the baseline screening within 1 year of commencing therapy (rather than requiring screening prior to initiation of treatment).

The recommendation for formal ophthalmic examination represents a significant shift from the previous guideline. The percentage agreement with this recommendation was the lowest of all recommendations within the guideline, reflective of the fact that several members of the GWG recognized the substantial organizational barriers to retinal screening alongside the absence of evidence that screening will definitely prevent retinal toxicity. In addition, it was acknowledged across the GWG that the estimated rates of HCQ retinopathy are substantially higher than the experience of anyone on the GWG, and the evidence was based upon lower-quality evidence (reflected in the GRADE score).

The impact of the guidelines from the American Academy of Ophthalmology in the USA has been evaluated. A predictive cost analysis suggested a 90% increase in comparison with the previous American Academy of Ophthalmology guidelines [61]. However, the same authors conducted a retrospective study of 183 follow-up patients and 29 new patients, and the actual cost increase was ~40% [61].

OCT is now the screening investigation of choice for macular degeneration in the UK and is routinely available in ophthalmology departments across the country. The cost implication for OCT screening is £32, while the cost of a full ophthalmological assessment (including slit-lamp examination and OCT) is £160 (based upon the payment by results tariff) [74].

A frequent question raised by rheumatologists involved in the development period of the guideline related to the potential for identifying incidental findings using OCT and whether background retinal disease would preclude HCQ therapy. It is important to highlight that OCT is a specialized ophthalmological assessment, which needs to be undertaken and reported upon by experts in the field. It would therefore not be the responsibility of the rheumatologist to act upon incidental findings (e.g. macular degeneration). With respect to the safety of commencing HCQ in a patient with pre-existing retinal disease, it should be borne in mind that pre-existing retinal disease is a risk factor for HCQ retinal toxicity. The clinical decision should then weigh up risks against the likely benefit of HCQ therapy, acknowledging its relatively modest anti-rheumatic effect (reflected in the EULAR recommendations advising use of HCQ monotherapy be limited to patients with very mild disease and contraindications to other agents) [75].

In summary, based upon the available evidence, the GWG felt that it was no longer appropriate to recommend Amsler grid assessment or simple visual acuity tests in the rheumatology outpatient clinic as part of baseline screening. Instead, formal retinal assessment is advised. In an ideal situation, this would include objective assessment using OCT. However, the GWG acknowledged that this recommendation has significant implications for local services. The Royal College of Ophthalmologists is currently undertaking its own formal review of the evidence, with a plan to develop national guidelines that appraise the evidence base in more detail, in particular evaluating cost implications. This current version of the BSR guideline has been written in collaboration with the Royal College of Ophthalmologists and will be updated to reflect any changes that arise from the future review.

Acknowledging the limitations of the clinical resources as well as the existing knowledge base, the current recommendation is worded in a manner that is compatible with the evidence but acknowledges organizational barriers.

Important unanswered questions that remain include: whether baseline OCT is needed in all patients (or at all); if the same screening recommendations are appropriate in younger adults with SLE; and does HCQ represent a cost-effect treatment in RA beyond 5 years if OCT is required?

Co-morbidities

(i) Pre-existing lung disease is not a specific contra-indication to DMARD therapy, but caution is advised when using drugs associated with pneumonitis in patients with poor respiratory reserve (GRADE 1B, 95%).

(ii) In patients with deranged liver biochemistry, hepatotoxic DMARDs should be used with caution, with careful attention to trends in test results (GRADE 1C, 100%).

(iii) In patients with impaired liver synthetic function (e.g. cirrhosis), DMARD therapy should be used with extreme caution (GRADE 1C, 97%).

(iv) Patients with chronic viral hepatitis infection should be considered for anti-viral treatment prior to DMARD initiation (GRADE 1B, 99%).

(v) DMARDs must be used with caution in chronic kidney disease (CKD), with appropriate dose reduction and increased frequency of monitoring (GRADE 1C, 97%).

(vi) Cardiovascular disease and prior malignancy are not considered contraindications to DMARD therapy (GRADE 1C, 95%).

Evidence supporting recommendations

Multi-morbidity is common in contemporary clinical practice, affecting >20% of the general population [27]. In rheumatic diseases, some co-morbidities are more prevalent because of complications of the underlying disease (e.g. renal disease in SLE) or shared risk factors (e.g. smoking). Co-morbid conditions can have significant implications for DMARD prescribing. It is beyond the scope of this guideline to review all co-morbidities. Attention will be paid to the most prevalent co-morbidities that have relevance to DMARD prescribing.

A large multinational study identified ischaemic cardiovascular disease (stroke and myocardial infarction; 6%) and prior solid malignancy (4.5%) as the most prevalent co-morbidities in RA [25]. Data from the British Society for Rheumatology Biologics Register confirmed the high prevalence of these diseases as well as highlighting co-morbidity particularly relevant to the UK, including asthma (10%) and COPD (5%) [76]. In addition to the above-mentioned co-morbidities, chronic liver disease and CKD will also be reviewed in light of their relevance to DMARD prescribing.

Recommendation: lung disease

The baseline screening for lung disease section of this guideline has already highlighted a change in recommendation regarding lung disease. Previous guidelines have singled out MTX specifically when considering pulmonary toxicity. Established lung disease has historically been considered an absolute contraindication to therapy with MTX. However, previous recommendations have been based upon low-quality evidence (observational studies and case reports). During recent years, there has been a growing perception that historical estimates of MTX-induced lung disease may have been overestimated, perhaps owing to channelling bias [28]. Two recent high-quality meta-analyses of RCT data from rheumatoid arthritis

and psoriatic arthritis have cast doubt upon the relationship between MTX use in rheumatic diseases and respiratory mortality [77, 78].

In a meta-analysis of RA trials, MTX use was associated with an increased risk of total infectious adverse respiratory events (Relative risk (RR) = 1.11, 95% CI: 1.02, 1.21), but was not associated with an increased risk of total non-infectious respiratory adverse events (RR = 1.02, 95% CI: 0.65, 1.60). A pre-specified subgroup analysis of studies in which pneumonitis was specifically reported revealed an increased risk in the group treated with MTX (RR = 7.81, 95% CI: 1.76, 34.72). However, the authors highlight an important caveat, which was that all reported cases of pneumonitis were from studies published prior to 2002. Among 2980 subjects randomized to MTX in randomized trials since 2002, there was not a single reported case of MTX pneumonitis. The authors speculated that the differential risk may reflect a change in the diagnostic scrutiny applied to MTX lung disease.

It is important that adverse events are not ascribed to a drug without adequate high-quality supporting evidence. In contrast to earlier studies suggesting respiratory toxicity from MTX, the Early RA Study found no evidence that MTX was associated with reduced survival among people with ILD [79]. Indeed, a small retrospective cohort study of patients with RA-ILD observed an improvement in forced vital capacity at 6 months in patients treated with MTX compared with either LEF or AZA [80]. These two examples are not intended to be interpreted as evidence that MTX is beneficial, but merely demonstrate the conflict of evidence that exists.

In addition, it is important to recognize that pulmonary toxicity is reported with almost all licensed DMARDs (see Table 2) [81].

Drawing all this information together is challenging. There is an association between MTX use and lung toxicity in the literature, although there is clearly disagreement among experts on the causal relationship and the magnitude of risk. In absolute terms, the risk is definitely small. In addition, MTX is a first-line DMARD in the treatment of RA, with a strong evidence base supporting its role not only in reducing disease progression but also in reducing overall mortality [82].

The consensus from the GWG was that, based upon existing evidence, pre-existing lung disease should not be considered an absolute contraindication to any DMARD. However, specific attention should be paid to assessment of baseline respiratory disease, acknowledging the association between ILD and rheumatic conditions. Alongside this, it is relevant to highlight the value of baseline lung function studies (rather than chest radiographs) as these help to identify patients with poor respiratory reserve, in whom a significant reduction in lung function would be potentially life threatening. Poor respiratory reserve will influence choice of DMARD and should prompt more vigilance for pulmonary toxicity. Decisions should be made on an individualized basis and with a full appreciation of the evidence base.

Table 2 Risk of pneumonitis reported by manufacturer

Drug	Pneumonitis listed in SPC
APL	No
AZA	Yes
CSA	Yes
Gold	Yes
HCQ	No
LEF	Yes
MTX	Yes
MCN	Yes
MMF	No (although cases reported)
SSZ	Yes
TCL	Yes

Mepacrine is not listed because no UK SPC is available. SPC: summary of product characteristics; TCL: tacrolimus; MCN: minocycline.

Recommendation: liver biochemical abnormalities

Chronic liver disease is a co-morbidity that is increasing in incidence in Europe [33]. The chief medical officer for England's annual report in 2012 highlighted liver disease as a growing clinical burden and public health priority in the UK [83]. Deaths from chronic liver disease in the under 65s in England increased by 20% from 2000 to 2009, making it the fifth leading cause of death. The major drivers of increasing liver disease are all potentially preventable: high alcohol consumption, obesity and chronic hepatitis B and C infection.

In patients with pre-existing liver biochemical abnormalities without evidence of cirrhosis (i.e. normal liver synthetic function), it is important to establish the underlying cause, prior to commencing DMARDs. Any underlying causes should be identified and managed. If this does not result in normalization of liver biochemistry or if no underlying cause of pre-existing liver enzyme elevations can be identified, discussing DMARD initiation with a gastroenterologist/hepatologist (including drug choice, lower starting dose and initially increased monitoring frequency) should be considered. Non-alcoholic fatty liver disease (NAFLD) is increasing in prevalence and is the most common cause of liver biochemical abnormalities [84]. Recommendations for the diagnosis and management of NAFLD exist, including when to refer for a specialist opinion [85].

Abnormal liver enzymes are not an absolute contraindication to any DMARD therapy, but preference should be given to a less hepatotoxic DMARD (e.g. SSZ), and more cautious monitoring is advisable. If DMARDs are used in patients with elevated liver enzymes, then particular attention to deteriorating trends in results is recommended.

Recommendation: liver failure

In patients with impaired liver synthetic function, the metabolism of many drugs is reduced and a risk of toxicity because of drug accumulation exists. With the exception of MMF, all the DMARDs referred to in this guideline undergo hepatic metabolism or bile conjugation and

clearance and, consequently, manufacturer SPCs uniformly recommend avoidance in patients with significant liver synthetic dysfunction. MMF clearance has been shown to be largely unaffected in patients with cirrhotic liver disease [86].

In case-by-case circumstances, clinicians and patients may decide that the risk/benefit ratio remains in favour of treatment even in the context of cirrhosis. An evidence base does not support such practice; however, it would be advisable to consider reductions in both dosage and frequency of administration.

In patients with impaired liver synthetic function, risk of DMARD toxicity is increased and, unless benefits clearly outweigh risks, DMARD therapy should be used with extreme caution (GRADE 1C, 97%).

Recommendation: viral hepatitis

Patients with chronic HBV infection are at risk of reactivation of HBV should they require immunosuppressive therapy. The level of risk depends both upon the degree of immunosuppression and upon the status of their HBV infection. Differing DMARDs confer variable levels of immunosuppressive effect. For example, HCQ and SSZ are comparatively less immunosuppressive, and in selected circumstances it may be appropriate to consider initiation of these agents in the face of active HBV infection.

Individuals with chronic HBV infection [hepatitis B surface antigen (HBsAg) positive and hepatitis B core antibody IgG (anti-HBc) positive], the serum HBV DNA levels can vary from undetectable (<20 international units/ml) to >1 000 000 000 (>9 $\log_{10}$) international units/ml depending on the balance between HBV replication and the immune response [87]. The majority of people who have serological recovery from HBV infection [HBsAg negative, hepatitis B surface antibody (anti-HBs) positive and anti-HBc positive] have undetectable HBV DNA in serum, but HBV persists in the liver, and its replication is controlled by the immune system [88, 89]. The balance between viral replication and immune control explains why immunosuppressive therapy can augment HBV replication in chronically infected persons and reactivate dormant HBV in individuals regarded as recovered. Some persons have so-called isolated anti-HBc status (presence of anti-HBc antibodies without HBsAg or anti-HBs antibodies), and most of them had past HBV infection and are at risk of HBV reactivation [90, 91].

Limited data exist assessing the effect of immunosuppression on Hepatitis C. Evidence that progression of cirrhosis is hastened is lacking, and treatment more challenging. However, despite absence of high-quality evidence, in an era of rapid advances in therapeutic options the advice remains to aim for viral control before immunosuppression.

Recommendation: CKD

CKD is highly relevant as a co-morbidity, as it has an impact upon prescribing for a majority of DMARDs. The 2010 Health Survey for England showed that overall, 6% of men and 7% of women had stages 3–5 CKD [92]. The survey also showed strong variation by age, with <1% of men and women aged 16–24 years at stage 3–5, but prevalence rose to 29% of men and 35% of women aged ⩾75 years. The 2007 NEOERICA study showed a prevalence of CKD stages 3–5 of 8.2% (10.6% females and 5.8% males) [93]. This study also showed that prevalence of CKD increases with age, with >70% of patients with diagnosed CKD being aged 65 years or older.

DMARD prescribing in patients with reduced renal function can give rise to problems for several reasons: DMARDs cleared via renal excretion accumulate, increasing the risk of toxicity; and DMARDs may be directly nephrotoxic.

It may be possible to avoid problems through dose reduction or use of alternative DMARD strategies. The impact of renal impairment on prescribing depends on the proportion of the drug eliminated by renal excretion and its toxicity. In addition, for DMARDs with a narrow safety margin or for patients at extremes of weight (BMI of $< 18.5\,kg/m^2$ or $> 30\,kg/m^2$), dose regimens based on creatinine clearance (e.g. using the Cockcroft and Gault calculation) should be used. When both efficacy and toxicity are closely related to plasma drug concentration, recommended regimens should be regarded only as a guide to initial treatment; subsequent doses must be adjusted according to clinical response and, where possible, plasma drug concentration.

Renal function declines with age; elderly patients frequently have some degree of renal impairment but, because of reduced muscle mass, serum creatinine may be within the normal range. It is wise to assume at least mild renal impairment when prescribing for the elderly.

Renal function in the UK is routinely reported in terms of estimated GFR calculated from a formula derived from the Modification of Diet in Renal Disease study (a formula that uses serum creatinine, age, sex and race), with values normalized to a body surface area of 1.73 m^2. Although Cockcroft and Gault calculations are superior in some patients, national reporting of calculated GFR makes this value more widely accessible. NICE guidance exists regarding the definitions of renal impairment (see Table 3).

Pre-existing impairment of renal function or impaired renal function identified at baseline assessment has important implications. Newly identified renal impairment should be investigated to identify an underlying cause and treated accordingly, in line with NICE guidance [94].

In addition to dose reductions in renal impairment, it is also appropriate to increase the monitoring frequency. No data are available to support specific recommendations for individual drugs; therefore, clinical discretion is advised. Nephrotoxic drugs should, if possible, be avoided in patients with renal disease because the consequences of nephrotoxicity are likely to be more serious when renal reserve is already reduced. Table 4 summarizes the information from the SPC for each DMARD. Where more than one manufacturer existed for a product, information from each manufacturer was reviewed.

Recommendation: cardiovascular disease and prior malignancy

Cardiovascular disease

Ischaemic cardiovascular disease is not a specific contraindication to any of the DMARDs included in this guideline. In fact, a recent meta-analysis from Canada revealed that MTX use is associated with a reduction in the risk of cardiovascular events in patients with either RA or PsA [95]. Likewise, prolonged use of other DMARDs, such as LEF and SSZ, has been suggested to reduce the risk of cardiovascular morbidity in patients with RA [96]. Indeed, there are numerous studies that have directly linked the disease activity burden of several rheumatic diseases to an excess cardiovascular risk. Therefore, control of the rheumatic disease should be seen as an important component of cardiovascular risk management, as recommended in EULAR guidance [97].

Malignancy

In patients with autoimmune rheumatic disease, the incidence of malignancy is increased. Susceptibility to neoplastic disorders is also increased in transplant recipients, which is considered to be a consequence of prolonged immunosuppression [98]. In particular, the occurrence of skin cancers is increased in patients on immunosuppression. However, despite numerous epidemiological studies, it remains unclear whether the increased risk of malignancy in patients with autoimmune disease is caused by the autoimmune disease itself or related to immunosuppression. Based upon the currently available evidence, prior malignancy cannot be considered a contraindication for treatment with DMARD therapy. It is important to acknowledge that the evidence base in this area is limited and clinicians must make individualized decisions. Certain examples exist where a DMARD is definitely implicated in a malignancy (e.g. MTX-induced lymphoproliferative disorder), and that DMARD should not be used again. Also, in patients with prior skin cancer, it may be appropriate to involve a dermatologist in the ongoing management, with consideration for enrolment in a formal skin screening programme. These situations highlight the limitations of blanket guidelines and serve as a reminder that clinicians must personalize care for each patient.

The incidence of *de novo* malignancy in patients on DMARDs for rheumatic diseases does not warrant a change to the current recommendations for surveillance for cancer in the general population. All patients should be made aware of existing national screening programmes that exist for cervical cancer, bowel cancer and prostate cancer.

Table 3 National Institute for Health and Care Excellence guideline CG182 renal function definitons

Degree of impairment	calculated GFR, ml/min/1.73 m^2
Normal, Stage I	>90 (other evidence of kidney damage)
Mild, Stage II	60–89 (other evidence of kidney damage)
Moderate, Stage III	30–59
Severe, Stage IV	15–29
Established renal failure, Stage V	<15

Data taken from [94].

Monitoring

Recommended DMARD blood monitoring schedule when starting or adding a new DMARD

(i) Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin every: 2 weeks until on stable dose for 6 weeks; then, once on stable dose,

Table 4 Recommended dose adjustment in chronic kidney disease

Drug	Accumulates in renal failure?	Nephrotoxicity	Chronic kidney disease stage		
			III	IV	V
			Recommended adjustment,% of standard dose		
APL	✓	✗	50	50	50
AZA	✗	✗	Normal dose	75–100	50–100
CSA	✗	✓	Normal dose	Normal dose	Normal dose
Gold	✓	✗	No data	No data	Avoid
HCQ	✓	✗	75%	25–50%	25%
LEF	✗	✗	Normal dose	Use with caution	Use with caution
MTX	✓	✓	50%	Contraindicated	Contraindicated
MCN	✓	✗	Use with caution	Contraindicated	Contraindicated
MMF	✓	✗	Normal dose	1 g twice daily maximum	1 g twice daily maximum
SSZ	Not reported in SPC	✗	Normal dose	Use with caution	Use with caution
TCL	✗	✓	Use with caution	Contraindicated	Contraindicated

Summary of product characteristics is available at www.medicines.org.uk [5] (accessed October 2015). TCL: tacrolimus; MCN: minocycline.

monthly FBC, creatinine/calculated GFR, ALT and/or AST and albumin for 3 months; and thereafter, FBC, creatinine/calculated GFR, ALT and/or AST and albumin at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity (GRADE 2B, 97%).

(ii) Dose increases should be monitored by FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks, then revert back to previous schedule (GRADE 2B, 97%).

(iii) Exceptions and additions to the monitoring schedule for specific DMARDs are included in the summary monitoring requirements Table 5 (GRADE 2B, 100%).

Evidence supporting recommendations

This section is referring to the laboratory monitoring of DMARD use, rather than the requirements for clinical monitoring of disease (which are addressed elsewhere [21]).

Frequency of monitoring blood tests

These guidelines set out to provide a standard monitoring template. It is essential that each patient is considered on an individual basis and monitoring frequency is appropriately reviewed. For example, in elderly patients, those with co-morbidity and polypharmacy, or those with a history of drug-related toxicity, more frequent monitoring may be appropriate.

There are numerous published schedules for monitoring immune modulatory therapies across multiple specialities. Recommendations vary by drug and by speciality prescribing. Looking across Europe and the USA, it is clear that there are also substantial differences in recommendations between countries. A difference between other national guidelines and previous UK guidance has been in the recommendations for monitoring of MTX. Previous UK guidance recommended monthly monitoring in stable patients, in contrast to every 12 weeks in the 2015 ACR guideline [99].

Previous BSR guidelines have recommended different monitoring schedules for each drug. This has led to confusion in both primary and secondary care, as well as amongst patients. The GWG agreed that a single recommendation for use across DMARDs, streamlining recommendations, would reduce confusion and lead to more consistent monitoring.

In addition, feedback from patient groups has been consistently to review the need for such frequent monitoring of DMARDs. Previous BSR/BHPR monitoring guidelines have advocated more frequent monitoring schedules than are recommended in other speciality areas using the same drugs (dermatology) and abroad (e.g. The Netherlands). Adopting a strategy with reduced frequency of monitoring investigations would not only be of value to patients but also have beneficial implications for service providers.

Therefore, the GWG set out to produce a single recommendation for monitoring all DMARDs, alongside conducting a critical appraisal of the evidence base for monitoring frequency. For comparison, commencing a patient on MTX 20 mg once weekly (without dose titration), the current guidelines recommend nine monitoring blood tests in the first 12 months *vs* 14 in the previous guideline. Commencing a patient on LEF 20 mg, the current guidelines recommend nine monitoring tests in the first 12 months, identical to the number recommended in the previous guideline (although the timing of the tests has been altered).

Table 5 Summary of monitoring requirements

Drug	Laboratory monitoring	Other monitoring
Apremilast	No routine laboratory monitoring	None
AZA	Standard monitoring schedule[a]	None
Ciclosporin	Extend monthly monitoring longer term[b]	BP and glucose at each monitoring visit
Gold	Standard monitoring schedule[a]	Urinalysis for blood and protein prior to each dose
HCQ	No routine laboratory monitoring	Annual eye assessment (ideally including optical coherence tomography) if continued for >5 years
LEF	Standard monitoring schedule[a]	BP and weight at each monitoring visit
Mepacrine	No routine laboratory monitoring	None
MTX	Standard monitoring schedule[a]	None
MTX/LEFcombined	Extend monthly monitoring longer term[b]	None
Minocycline	No routine laboratory monitoring	None
Mycophenolate	Standard monitoring schedule[a]	None
SSZ	Standard monitoring schedule for 12 months then no routine monitoring needed	None
Tacrolimus	Extend monthly monitoring longer term[b]	BP and glucose at each monitoring visit

[a]Standard monitoring as per sections (i) and (ii) of the recommendations for DMARD blood monitoring. [b]Patients who have been stable for 12 months can be considered for reduced frequency of monitoring on an individual patient basis. BP: blood pressure.

Appraisal of the evidence base

The evidence base for selecting specific monitoring schedules is weak. Few studies have evaluated different monitoring schedules; however, there are many trials that have reported the incidence of adverse effects with individual therapies, which can help to guide monitoring schedule choice.

MTX is the most frequently prescribed DMARD in rheumatic disease now [100–103]. For this reason, the greatest evidence base for toxicity is available for this agent. Early studies from before 1980 in the dermatology literature described severe liver disease, including cirrhosis, in patients with psoriasis treated with MTX [104]. There was initial concern that liver biochemistry testing was unable to predict actual liver toxicity. Thus, in the past, the dermatology community recommended monitoring for liver disease by liver biopsy [105]. Potential limitations of the studies on which the past recommendations were based included the performance of blood sampling only on the day of the liver biopsy and the lack of control for exposure to other hepatotoxins (such as alcohol). When rheumatologists began using MTX for patients with RA, Kremer *et al.* [106, 107] undertook two sentinel prospective studies, in which baseline and follow-up liver biopsies were performed. In contrast to the dermatology studies that performed blood sampling only on the day of liver biopsy, Kremer *et al.* measured the AST at frequent intervals between sequential biopsies and demonstrated that liver enzyme elevations were predictive of liver biopsy findings. Additionally, the studies of Kremer *et al.* showed that in patients who had their MTX dose adjusted in response to liver test abnormalities, no significant deterioration was noted on subsequent biopsy findings [107]. For this reason, liver biopsy ceased to be recommended as part of routine monitoring of MTX.

Evidence of toxicity from RCTs

Numerous trials (including many of the anti-TNF studies) provide robust data with serial laboratory monitoring of patients receiving DMARDs, especially MTX, both as incident and prevalent users. Studies reporting on laboratory adverse events were systematically reviewed to extract data pertaining to MTX, acknowledging that this is the most frequent DMARD used in practice. Where relevant, literature has also been searched for other DMARDs.

Justification for more intense monitoring during initiation

Bathon *et al*. [108] published an RCT comparing etanercept with MTX. This trial provides information on 217 incident MTX users followed up for 12 months. They treated 632 patients with early RA with either twice-weekly s.c. etanercept (10 or 25 mg) or weekly oral MTX (mean, 19 mg/week) for 12 months. The frequency of any abnormal laboratory results was similar in all groups. However, approximately twice as many patients in the MTX group as in the group assigned to receive 25 mg of etanercept had high serum AST concentrations (32 *vs* 16%, $P < 0.001$) or high serum ALT concentrations (44 *vs* 24%, $P < 0.001$).

The PREMIER study provides data on incident MTX use [109]. In addition to the primary publication, full data regarding the incidence of adverse events are reported online [110]. A significant increase in ALT was reported in 17/257 (6.61%) MTX monotherapy users, 7/274 (2.55%) adalimumab users and 29/268 (10.82%) patients on combination therapy.

Emery *et al.* [111] published a trial of golimumab, recruiting MTX-naïve subjects and randomizing them to MTX, golimumab or combination therapy. The rates of ALT elevation were 10/160 (6.3%) on MTX monotherapy, 27/317(8.5%) on MTX/golimumab combinations and 7/157 (4.5%) on golimumab monotherapy. Kay *et al.* [112] published a randomized trial of golimumab in 2008 that enrolled a cohort of MTX prevalent users. Again, rates of liver enzyme elevation were low, with 1/34 (2.9%) patients on MTX monotherapy and 9/137 (6.6%) patients on MTX and golimumab combination developing an elevation of ALT >2 times the upper limit of normal. These data show that 3–44% of new starters of MTX experience liver enzyme elevations.

Justification for reduced frequency monitoring once stable

The ARMADA trial recruited 271 prevalent MTX users and reported a very low incidence of laboratory abnormalities over 24 weeks of follow-up [113]. Keystone *et al.* [114] reported on 619 prevalent MTX users randomly assigned to receive additional placebo or adalimumab, and during 52 weeks of follow-up there were no serious liver-related adverse events reported in any group.

Observational data from 248 prevalent MTX users revealed severe laboratory abnormalities occurring in 2.9% of patients per year, with 0.9% developing AST elevations >80 U/l [115]. No apparent change in risk over time was observed.

It is predictable that studies of prevalent users would report a lower incidence of adverse events owing to the healthy user phenomenon. Patients who are at higher risk of liver toxicity from MTX will develop biochemistry abnormalities earlier on during treatment and subsequently be taken off treatment. Patients who remain on treatment by 12 months are in effect self-selected healthy users.

Predictors of liver toxicity with MTX include lack of folate supplementation and coexistent fatty liver disease.

Data from the Mayo Clinic cohort in Rochester also used routine data to explore predictors of MTX-related laboratory abnormalities [116]. Four hundred and eighty-one patients were followed for 2323 person-years of MTX exposure. MTX was discontinued permanently because of abnormal laboratory test results in 22 patients (4.6%), the majority of whom (17/22) had abnormal liver biochemistry. Predictors of a significantly higher percentage of abnormal AST values included lack of folate supplementation ($P < 0.001$), increased creatinine ($P < 0.03$), presence of untreated hyperlipidaemia ($P < 0.02$) and male sex

($P < 0.04$). The authors hypothesized that underlying non-alcoholic fatty liver could be an important risk factor for MTX-related liver toxicity. This hypothesis is supported by similar findings from analysis of Veterans Health Administrative Records in the USA [117]. Six hundred and fifty-nine incident users of MTX were studied and found to have a 6% incidence of moderate ($\geqslant$1.5 times the upper limit of normal) elevations in AST or ALT over a mean follow-up of 7 months. Predictors of moderate transaminase elevations included obesity and elevated total cholesterol. Other identified predictors included concomitant use of biologic agents and lack of folic acid supplementation. Gender was not assessed given that the Veterans cohort is predominantly male.

Hepatotoxicity with other DMARDs

Acute clinically relevant liver injury secondary to SSZ use has been estimated to occur in 0.001–0.004% based upon population-based case–control studies [118, 119]. The majority of cases occurred within the first month of starting SSZ therapy. Notably, ~25% of patients were jaundiced at presentation, and a proportion of these rapidly developed hepatic failure. These cases may have reflected hepatotoxicity as a component of the drug rash, eosinophilia, systemic symptoms syndrome, of which SSZ is one of the most common precipitants [120].

Smolen *et al.* [121] published an RCT comparing 133 patients assigned to LEF with an equal number assigned to SSZ plus 92 subjects assigned to placebo. Two patients in the LEF group, one in the placebo group and two in the SSZ group were withdrawn because they had abnormal results on liver function tests. Very abnormal values (three or more times the upper limit of normal) in liver function tests were observed in three LEF-group patients and five SSZ group patients, but none in the placebo group.

A second major LEF trial was published in the same year, which randomly assigned 999 patients to either LEF or MTX [122]. Clinically relevant elevations in plasma liver enzyme concentrations ($\geqslant$3 times upper limit of normal) were noted in 32/501 (6.4%) subjects receiving LEF and 124/498 (25%) subjects treated with MTX for 1 year. During the second year of treatment, 16/292 (5.4%) subjects treated with LEF and 20/320 (6.3%) subjects taking MTX had clinically relevant elevations in plasma liver enzyme concentrations.

Observational data sets have confirmed a lower incidence of liver enzyme abnormality with LEF compared with MTX [123]. Despite this, the LEF SPC recommends blood tests every 2 weeks for the first 6 months, then alternate months thereafter.

There are undoubtedly differences in the incidence of hepatotoxicity across the DMARDs. However, the consensus of the GWG was that it was appropriate to align the monitoring schedule for MTX, SSZ and LEF, despite this contradicting the wording of individual SPCs. The rationale for a harmonized monitoring pathway has already been explained. In patients with identified liver disease, more frequent monitoring schedules are appropriate to consider.

Defining patients at higher risk of toxicity

The monitoring recommendations outlined in this guideline represent a minimal monitoring schedule. Essential to the recommendation for reduced frequency monitoring schedules is the inclusion of the statement that more frequent monitoring is appropriate in patients at higher risk of toxicity. Recognition of patients at increased risk of complications remains a clinician judgement that will depend upon a multitude of factors, including a patient's prior history of adverse drug events, their medical co-morbidities and also the co-prescription of medications that may interact with a DMARD.

Factors to consider when judging if a patient is at high risk of DMARD toxicity are as follows: extremes of weight (BMI $<$18 or $>$30 kg/m^2); renal impairment (CKD three or higher); pre-existing liver disease (e.g. NAFLD); significant other medical co-morbidity (e.g. malignancy); old age ($>$80 years); and previous DMARD toxicity.

The evidence base for factors predicting adverse events with DMARD use is limited. The list here should act as a template for factors to consider rather than be viewed as a comprehensive document. Individual clinician judgement remains central to decisions, with personalized treatment plans remaining at the heart of the treatment pathway. It would be wrong to infer from this document that all patients with a BMI $>$30 kg/m^2 should receive more intensive treatment monitoring. Likewise, judgements based solely upon age are inappropriate, and a more holistic assessment of frailty is more relevant. Definitive lists cannot capture the essence of clinical judgement, and this highlights the importance of recommendation (i) of the generic recommendations before commencing any DMARD that states DMARD initiation should take place under the supervision of an expert in the management of rheumatic diseases.

Exceptions to the standard schedule

Recommended exceptions to the standard schedule are summarized in tabular format in the summary recommendations (Table 5). The recommendations are as follows.

(i) APL, HCQ, MCN and mepacrine do not require routine laboratory monitoring (GRADE 2C, 98%).
(ii) SSZ does not need routine monitoring once patients are stable for 12 months (GRADE 2B, 98%).
(iii) Monthly monitoring longer term (at least 12 months) should continue for MTX/LEF combinations, CSA- and TCL-based regimens (GRADE 2B, 100%).
(iv) Patients remaining on HCQ for $>$5 years should be offered annual eye assessments to screen for retinal toxicity (ideally including OCT) (GRADE 1B, 93%).
(v) Patients receiving LEF/CSA/TCL should have their BP assessed at each monitoring visit; patients on TCL/CSA should also have glucose measured; patients on LEF should also have weight measured (GRADE 2C, 97%).

(vi) Monitoring of therapeutic drug levels should be considered for patients receiving TCL and CSA (GRADE 2C, 94%).
(vii) Patients receiving gold therapy should have urinalysis for blood and protein prior to each dose (GRADE 2C, 96%).

Evidence supporting recommendations

DMARD regimens without need for routine laboratory monitoring

In accordance with SPC information, the following DMARDs have no laboratory monitoring requirement according to existing product information: APL, HCQ, MCN and mepacrine. Routine SSZ monitoring can be discontinued once treatment has been stable for 12 months. However, alongside the recommendation that more frequent monitoring is appropriate in patients at higher risk of toxicity, the decision to discontinue monitoring should be personalized to each individual patient (e.g. taking into account their renal function).

Monthly monitoring required longer term

Kremer *et al.* [124] published a trial of combination MTX and LEF. The addition of LEF in stable MTX users resulted in 6/30 (20%) subjects developing ALT elevations >2 times the upper limit of normal. This observation of an increased rate of liver enzyme abnormalities in patients on combination MTX and LEF has been replicated by work from Curtis *et al.* [123] using the Corrona database in the USA as well as in an Australian retrospective cohort study [125]. These studies demonstrate occurrence of liver enzyme abnormalities beyond the early months of treatment and therefore support the recommendation for ongoing monthly monitoring for patients on MTX and LEF.

The evidence for other combination strategies was also reviewed. MTX with SSZ and/or HCQ has been studied in several randomized trials. Four studies found no difference in the rate of laboratory abnormalities [126–129]. A single study by Dougados *et al.* [130] reported a higher incidence of liver biochemistry abnormalities with MTX and SSZ combination. Two hundred and nine patients were enrolled and randomized to MTX alone, SSZ alone or a combination of MTX and SSZ, with 52 weeks follow-up. ALT elevations were observed in none on SSZ monotherapy, one on MTX monotherapy and 6 (9%) on combination therapy. Data from studies beyond 52 weeks were not available.

Therefore, the GWG felt that there was insufficient evidence to recommend routine monthly monitoring for combinations other than MTX and LEF.

The use of TCL and CSA in rheumatic diseases has increased in recent years, particularly within the field of CTD and idiopathic inflammatory myositis. However, experience of long-term safety of these agents comes primarily from other therapeutic areas (especially transplant medicine) and therefore guidelines from other disciplines have been reviewed [131–134].

Following transplantation, the SPCs for TCL and CSA recommend that monitoring on a routine basis includes: blood pressure, ECG, blood glucose, electrolytes (particularly potassium), liver and renal function tests and haematology parameters. It is notable that in neither the SPC nor in any of the published guidelines within PubMed is a specific monitoring frequency recommended. In general, monitoring frequency is assumed to align with the frequency of clinic visits (which tend to be very frequent in the early transplant period) and reduce to 3 monthly or less once patients are stable and beyond 12 months post procedure.

In the absence of an evidence base, and acknowledging that these DMARDs are often used to treat patients with diseases that require more frequent clinical review for other reasons, the recommendations from the GWG are to monitor the induction phase in line with other DMARDs, and then to continue monitoring for TCL and CSA monthly for at least 12 months after initiation. Beyond 12 months there are few data to provide support to any recommendations. In transplant medicine, blood monitoring frequency reduces in stable patients to every 2–3 months.

Other monitoring required

The evidence base surrounding HCQ and retinopathy has been discussed already in the drug-specific recommendations section. Screening for retinal disease aims to pick up preclinical disease before an irreversible retinopathy develops [71, 72, 135]. The risk of ocular toxicity starts to rise after the first 5 years of treatment [73]. In the largest study to date, HCQ toxicity in patients with >5–7 years exposure has a prevalence of ~1% [65]. The limitations of standard ocular screening in clinic with Amsler grids or visual acuity testing have already been discussed. Therefore, in line with guidance from the ACR, the GWG felt it appropriate to recommend that annual screening commence after 5 years of treatment. In line with the screening practice at baseline, formal retinal assessment is the preferred approach, ideally incorporating spectral domain OCT.

This recommendation reflects a significant change from previous guidelines and will have a potential impact on ophthalmology services in local areas and therefore rheumatology departments are encouraged to ensure that engagement with ophthalmology services within their region occurs to facilitate appropriate monitoring of HCQ.

Additional monitoring for LEF/CSA and TCL

Additional laboratory monitoring is recommended for specific DMARDs. The rationale for extra investigation reflects experience from other speciality areas (especially transplant medicine). However, the relevance of such recommendations to rheumatology practice is not entirely clear given that the background risk of complications may differ, and different doses of the drugs may be used.

SPC recommendations for TCL and CSA advocate the need for a baseline ECG and subsequent monitoring of blood pressure. This relates to the risk of left ventricular

hypertrophy with calcineurin inhibitors. Hypertension is also a recognized side-effect of LEF therapy [136].

A notable addition to the monitoring schedule is the advice for blood glucose monitoring for TCL and CSA. An increased incidence of impaired glucose tolerance occurs on treatment with TCL [137]. The association has also been observed with CSA, although to a lesser extent [137].

The majority of the data relating to the calcineurin inhibitors comes from renal transplant studies. In a retrospective study of 11 659 patients, the incidence of new-onset diabetes post-transplantation was 9.1, 16 and 24% at 3, 6 and 12 months post-transplant, with the risk increased with TCL (relative risk 1.53) [137].

There are minimal data for the risk of diabetes with TCL in rheumatic disease. A meta-analysis of TCL treatment compared with CYC in LN included a total of 188 patients and showed a non-significant increase in the risk of hyperglycaemia: 1.4 (95% CI: 0.67, 2.92) [139]. In a Japanese post-marketing surveillance study of 3172 patients with RA on TCL for up to 24 weeks, diabetes was reported in 1.5% [140]. This lower incidence is perhaps attributable to the low doses of TCL used, with an average dose <2 mg/day, lower doses being associated with a lower incidence of diabetes [141].

As such, although there is no definitive evidence to quantify the risk in rheumatic disease there does appear to be an increased risk of diabetes in patients treated with TCL. Given the baseline increased risk of cardiovascular disease in patients with inflammatory rheumatic diseases, it is important promptly to identify and minimize the additional risk posed by drug-induced diabetes. The risk is greater in patients with concomitant steroid therapy and other risk factors, including Afro-American race, older age and high BMI [138, 142].

The guideline specification of glucose measurement does not specify what test should be used. It is up to local practice to use a measure that balances what is feasible and reliable. In an ideal setting, a fasting serum glucose would be preferred. Alternatives include a non-fasting sample (but this will identify false positives) or glycated haemoglobin (A1C). A UK expert advisory group endorsed the World Health Organization recommendation that the haemoglobin A1C can be used as a diagnostic test for type 2 diabetes (with levels above 6.5% indicating diabetes) [143]. However, the A1C test has important limitations relevant to patients with rheumatic disease: it is inaccurate in settings of anaemia and renal failure; and it is insensitive to rapid changes in glucose (e.g. with CS use). These factors should be taken into consideration when selecting the appropriate screening tool for individual patients.

Finally, the GWG acknowledged that some centres routinely monitor magnesium concentrations in patients on calcineurin inhibitors (especially TCL). Magnesium is not usually included in routine clinical chemistry results; however, clinicians prescribing calcineurin inhibitors should be aware of this potential toxicity.

LEF has been associated with significant weight loss in some individuals and, in accordance with the SPC, it is recommended to include assessment of weight within the monitoring schedule.

Therapeutic drug monitoring

In transplantation medicine, therapeutic drug monitoring for CSA and TCL is the standard of care and recommended in national guidelines [131, 133]. Therapeutic drug monitoring is valuable for agents with narrow therapeutic windows as well as medication prone to drug–drug interactions; calcineurin inhibitors fit into both of these categories. Indeed, both TCL and CSA are metabolized by the cytochrome P450 pathways, as well as being influenced by ATP binding cassette activity for absorption and excretion. Therefore, co-prescription of other medications that share or interact with these metabolic pathways has the potential to shift TCL/CSA drug concentrations outside of the therapeutic window.

In terms of defining the therapeutic window using plasma concentrations, the upper range of drug concentrations has been more clearly defined. TCL blood concentrations >15 ng/ml are correlated with toxicity [144]. However, it is important to note that toxicity can occur for both TCL and CSA even when drug concentrations remain within therapeutic ranges.

In transplantation medicine, the lower end of the therapeutic window has been defined more clearly, enabling clinicians to use drug concentrations to guide efficacy [132]. In rheumatic disease, lower drug doses are used, and data do not exist correlating drug concentrations with efficacy; therefore, less frequent TCL concentrations may be appropriate.

Monitoring for renal disease with gold therapy

Long-term exposure to gold salts is associated with a risk of nephrotoxicity in up to 10% of patients [145]. Renal toxicity usually manifests with an insidious development of proteinuria that is reversible with withdrawal of therapy [145]. Therefore, recommendations for urinalyis prior to each dose remain unchanged from previous BSR DMARD monitoring guidelines.

Perioperative management

Perioperative DMARD management

(i) Steroid exposure should be minimized prior to surgical procedures, and increases in steroid dose to prevent adrenal insufficiency are not routinely required (GRADE 2B, 95%).

(ii) DMARD therapy should not routinely be stopped in the perioperative period, although individualized decisions should be made for high-risk procedures (GRADE 2B, 95%).

Evidence supporting recommendations

Surgical procedures are an important consideration for patients with rheumatic diseases. In particular, patients with rheumatic diseases frequently require orthopaedic interventions. Consideration of DMARD management in

the perioperative period is important. Among patients with RA, 75–84% of patients undergoing arthroplasty are receiving DMARDs [146]. In addition, a majority of RA patients are on CSs at the time of arthroplasty [147].

Stopping or continuing DMARD therapy requires balancing the risk of disease flare with the risk of infection. RA flares develop in 10–20% of patients undergoing surgery and have a potential to impact adversely on postoperative recovery [148, 149]. In addition, active RA increases infection risk, further complicating decisions regarding DMARD interruption [150].

Recommendation: perioperative steroid exposure

Although this guideline is not specifically concerned with CS therapy, it is relevant to mention this in the context of perioperative RA management. The infection risk associated with use of CSs is high, even at low dose [151]. Traditional teaching advocated DMARDs be discontinued in the perioperative period and the dose of CSs increased to limit RA flares and also prevent secondary adrenal insufficiency during a period of stress. There is little evidence to support this practice. Two small, randomized, double-blind, controlled trials demonstrated that patients receiving their usual steroid dose (between 5 and 16 mg prednisolone daily) at the time of surgery responded with an appropriate increase in cortisol, and haemodynamic status was not affected [152–155]. Other observational studies are consistent with these findings, with patients with secondary adrenal insufficiency undergoing various major surgical procedures (e.g. nephrectomy) taking their usual daily dose of CS without perioperative hypotension [156–158]. Albeit limited in size, these studies suggest that steroid doses need not be increased in the perioperative period.

Recommendation: perioperative DMARD therapy

MTX use in the perioperative period has been studied in two controlled trials. In a prospective RCT of 388 patients with RA undergoing orthopaedic surgery, patients were randomized to continue or interrupt MTX therapy [159]. Fewer complications were observed in patients who continued MTX. A second trial enrolled 64 RA patients and reported no difference in wound health compared with patients in whom MTX was withheld [160]. Neither study considered the influence of co-morbidities or underlying disease severity. In addition, typical MTX doses were low (<15 mg/week).

A number of observational studies have also evaluated perioperative MTX use. One study examined withheld and continued MTX use perioperatively and compared these patients with those not prescribed MTX [161]; a second study used the Veteran Affairs database to look at the relationship between interruptions in pharmacy collection of DMARDs in the perioperative period and surgical site infection [162]. Neither study found any association between DMARD interruption and infection risk. A retrospective review specifically exploring the association between MTX and hand or wrist surgery complications also found no evidence of any adverse effect of continuing MTX in the perioperative period [163].

Some data suggest that not all DMARDs carry equivalent infection risk profiles. The infection risk with LEF may be greater than for MTX [164, 165]. Information available regarding perioperative use of LEF is conflicting; one study describes significantly more wound complications in patients taking LEF at the time of elective orthopaedic surgery compared with patients receiving MTX [166]. A second study compared patients who continued *vs* discontinued LEF for 4 weeks prior to surgery and reported no difference between groups [167].

The elimination half-life for LEF is ~2 weeks; therefore, in order to eliminate exposure to LEF a prolonged period (five half-lives) off the drug would be required (or a washout procedure undertaken). Therefore, in the absence of clear evidence to support an interruption of treatment, the same recommendation is applied to LEF as for MTX.

There are limited data available regarding use of HCQ, AZA or SSZ and perioperative infection. A retrospective study of 367 joint surgeries in 204 RA patients, two-thirds receiving DMARDs including HCQ and AZA, demonstrated no association with perioperative infection [168, 169].

It is noteworthy that there are some contradictory data regarding interruption of immune suppression in the perioperative period. A cohort study examined the risk factors associated with postoperative prosthetic joint infection in patients with RA undergoing knee or hip replacement; the perioperative use of DMARDs was examined [170]. Stopping DMARD therapy at the time of surgery lowered the risk of subsequent prosthesis infection (Hazard ratio (HR) = 0.65, 95% CI: 0.09, 4.95), but this was statistically not significant. This study included all DMARDs, including biologic agents, and therefore does not present sufficiently robust evidence to alter the recommendation.

Information regarding MMF and TCL ia lacking in patients with rheumatic disease. Patients receiving these medications in the post-transplant setting routinely continue these agents in the perioperative period.

Given these data, it is recommend that all DMARDs can be continued during the time of surgery. This recommendation is in keeping with other national and international published guidance (including previous BSR guidance) [4, 171, 172].

Attention to renal function, however, is important so that inadvertent drug accumulation does not occur. In addition, in surgical settings where there is a high risk of infection, decisions should be made on an individual basis and consideration be given to interruption of DMARD therapy (for 2 weeks prior to surgery and restarted once wound healing is satisfactory). High-risk surgical procedures include class 3 or 4 surgical procedures (i.e. contaminated or dirty procedures [173]) and longer procedures (e.g. duration >60 min) [174]. In addition, patient factors, such as age and co-morbidity, also increase surgical infection risk and should be considered on an individualized basis [174].

Intercurrent infections

I. During a serious infection, MTX, LEF, SSZ, AZA, APL, MMF, CSA and TCL should be temporarily discontinued until the patient has recovered from the infection. (GRADE 1A–1C, 97%).

Evidence supporting recommendations

Recommendation: intercurrent infections

Patients with inflammatory arthritis have a higher risk of developing serious infections, and this risk appears to be increased most in patients with RA [165, 175–178]. In this context, serious is defined as an infection that warrants admission to hospital or parenteral anti-microbial therapy.

A population-based study reported a 70% increase in infections and an 85% increase in infections requiring hospitalization in an inception cohort of 609 patients with RA compared with age- and sex-matched population controls [179]. The infection risk appears to be particularly elevated in patients with co-morbidities, with use of CSs and with increased disease activity. A prospective analysis of 6242 RA patients on stable therapy (>6 months) revealed that each 0.6 U increase in DAS28 score corresponded to a 4% increased rate of outpatient infections (Incidence rate ratio (IRR) = 1.04, P = 0.01) and a 25% increased rate of infections requiring hospitalization (IRR = 1.25, P = 0.03) [150]. In contrast, an increased infection risk is a consequence of (prolonged) immunosuppressive treatment. Immunosuppressive DMARDs used in inflammatory arthritis are characterized by their different modes of action and are associated with an enhanced risk of developing or recovering from an infection. The majority and the largest studies investigating the association between DMARD use and infection risk have been performed in patients with RA.

A meta-analysis of seven trials including a total of 732 RA patients evaluated efficacy and safety of MTX treatment *vs* placebo. This analysis showed that patients who received MTX were more likely to have an infection when compared with patients who received placebo, at 12–52 weeks (49 *vs* 35%; RR = 1.3, 95% CI: 1.0, 1.6) [180]. Similar results of an increased risk of infection have been reported for LEF, SSZ and AZA in patients with RA [176, 181–184].

The long-term (52-week) results of a phase III RCT of APL in patients with psoriatic arthritis showed that upper respiratory tract infections and nasopharyngitis occurred in > 5% of treated patients [185, 186]. It should be noted that although the safety data for APL appear to be encouraging, the data generated thus far have come from clinical trials only and are of relatively short-term exposure (1–2 years).

Studies investigating the infection risk of MMF, CSA or TCL in patients with inflammatory arthritis are limited. The majority of safety data stem from studies in patients with lupus and transplant recipients and indicate that use of these drugs is also associated with an increased risk of developing an infection [187–189]. There is no evidence to suggest the use of HCQ, MCN or gold treatment in inflammatory arthritis is associated with an increased risk of infection [175, 190–192].

Taken together, patients with inflammatory arthritis are more susceptible to intercurrent infections. Drugs with immunosuppressive properties are likely to contribute to this propensity. Consistent with the precautions described in the medicines compendium, these intercurrent infections may be more severe in nature and may, therefore, require early and vigorous treatment. In addition, in patients with a serious infection (e.g. infection requiring i.v. antibiotics or hospitalization), MTX, LEF, SSZ, AZA, APL, MMF, CSA and TCL should be discontinued temporarily until the patient has recovered from the infection. It can be considered appropriate to continue these drugs in patients with minor infections (e.g. uncomplicated urinary tract infection treated with a short course of oral antibiotics). MCN, HCQ and gold treatment can be continued during minor and severe infections.

Shared care agreements

Shared care recommendations

(i) The prescriber has responsibility for ensuring patients are adhering to monitoring guidance (GRADE 1C, 97%).

(ii) When prescribing takes place in primary care, it should be supported by local written shared care agreements highlighting responsibilities of each party (patient, secondary care, primary care) (GRADE 1C, 97%).

(iii) Contact rheumatology team urgently and consider interruption in treatment if any of the following develop (see also Table 6): white cell count $<3.5 \times 10^9$/l; mean cell volume >105 f/l; neutrophils $<1.6 \times 10^9$/l; creatinine rise >30% over 12 months and/or calculated GFR <60; unexplained eosinophilia $>0.5 \times 10^9$/l; ALT and or AST >100 U/l; platelet count $<140 \times 10^9$/l; inexplained reduction in albumin <30 g/l (GRADE 1C, 99%).

As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g. gradual decreases in white blood cells (WBC) or albumin, or increasing liver enzymes).

For clinically urgent abnormalities, emergency access to specialist rheumatology advice, with response within one working day, should be available as per NICE guidelines.

Evidence supporting recommendations

Recommendations: shared cared agreements

Optimal prescribing of DMARDs needs to consider several factors, including speed of initiation, safety and patient convenience.

Several possible models exist for prescribing DMARDs: entire management in secondary care; entire management

Table 6 Laboratory abnormalities requiring action

White cell count $<3.5 \times 10^9$/l	Mean cell volume >105 f/l
Neutrophils $<1.6 \times 10^9$/l	Creatinine increase >30% over 12 months and/or calculated GFR <60 ml/min/1.73 m^2
Unexplained eosinophilia $>0.5 \times 10^9$/l	ALT and/or AST >100 U/l
Platelet count $<140 \times 10^9$/l	Unexplained reduction in albumin <30 g/l

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GFR: glomerular filtration rate.

in primary care; and initiation in secondary care followed by maintenance in primary care.

Each model has potential advantages and drawbacks. In the context of early inflammatory arthritis, NICE guidelines recommend DMARD initiation in a timely fashion [193]. For this reason, there may be an advantage of DMARD initiation taking place in secondary care, where rapid review of baseline investigations is possible and where dedicated support structures exist for drug education.

However, in an ideal situation, a patient would only have a single prescribing record (rather than separate records in primary and secondary care). Multiple prescribing records are a particular issue for patients with other coexisting long-term conditions. Although a unified care record may become available in future, few secondary care centres currently have access to primary care records or vice versa. Separate prescribing arrangements increase the risk of inadvertent drug interactions (e.g. MTX and trimethoprim).

In existing circumstances, there is an advantage to maintaining all long-term prescribing in primary care. However, other factors that may influence prescribing patterns include locality of phlebotomy services or availability of monitoring resources (e.g. electronic record-based monitoring systems). Recommending a single model of care at a national level is therefore not appropriate.

Prescribing DMARDs requires various aspects of monitoring to be undertaken (e.g. blood tests). One central recommendation is that the team responsible for prescribing the medication should also hold responsibility for monitoring. This is in line with specific recommendations from the National Patient Safety Agency (NPSA) [194].

MTX is the most widely prescribed DMARD, and additional mention of this agent is warranted. Acknowledging some of the specific requirements of treatment (weekly dosing, routine monitoring, etc.), it is not surprising that problems with prescribing can occur. Data from the NPSA National Reporting and Learning System identified MTX in the top five of medicines associated with patient harm based upon repeated reports of patient safety incidents. Data provided by the NHS Litigation Authority and the medical and pharmaceutical indemnity associations (The Medical Defence Union, Medical Protection Society, and Chemists' Defence Association), confirmed this [194]. Collectively, 94 cases (1993–2002) were identified that had resulted in claims against clinicians. The most frequent reason for a claim was overdose of the drug, usually because a weekly dose had been prescribed as a daily dose, and usually by the patient's GP. These data obviously relate only to incidents of harm, and the true incidence of adverse events is likely to be underestimated.

Therefore, the prescribing of MTX has been subject to a review by the NPSA. During the review, it was apparent that clinical practice varied significantly across the NHS. This was particularly evident through a plethora of local shared care guidelines and general inconsistency toward monitoring responsibility. The guidelines were predominantly focused upon transfer of prescribing from the secondary care specialist to the primary care GP, and neither the guidelines nor the specialists' discharge letters contain explicit instructions regarding the monitoring schedules, responsibility for conducting the monitoring tests and review of results, including action to be taken if results are outside of the norm. Likewise, guidance on the length of period for supply of medication between blood testing, and communication of changes in dosage directions were also found to be lacking. Following discussions with the relevant clinical groups and the NPSA, a checklist for positive practice was proposed to provide a consistent approach.

NPSA MTX safe prescribing practice checklist

When initiating treatment, information is available to provide to the patient on the risks and benefits of this medicine, confirmation of patient understanding/consent, baseline tests conducted, monitoring need and schedule explained to the patient [194]. A patient-held recording document is issued and its use explained.

Issues to be addressed within Shared Care Guidelines are the clarity of 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, and 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. The BSR has published guidelines for the monitoring of disease-modifying drugs, including MTX, which may be a useful source of information.

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. Changes to printer driver software to shade prescription signature space on FP10 or WP10 to alert the prescriber to high-risk drugs might also help in this instance.

Beware patients attending with other symptoms; signs of MTX toxicity or intolerance may present as, for example, breathlessness, dry persistent cough, vomiting and diarrhoea.

Patients receiving MTX may be admitted to any ward or receive outpatient treatment for coexisting conditions, and staff in all areas may therefore be involved in continuity of prescribing, monitoring or administering MTX as a result. 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 6 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.

Alongside these recommendations, the GWG felt it important to highlight that in the UK tablets of 2.5 and 10 mg are available, and confusion between these strengths has the potential to result in harm. Therefore, particular attention should be paid to the strength of formulation supplied.

Finally, it is relevant to be aware that although the above NPSA recommendations were primarily aimed at oral MTX, multiple devices are now available for parenteral use. As each brand of device differs, it is essential that patients receive adequate training on the specific device prescribed and that switching between devices should be supported by appropriate patient counselling and education.

Recommendation: responding to laboratory abnormalities

Table 6 summarizes laboratory abnormalities that should trigger action. The management of the patient who experiences laboratory abnormalities during DMARD therapy is beyond the scope of these guidelines. Decisions should be made on a case-by-case basis and without assuming that abnormalities are always attributable to the DMARD. It is also appropriate for cut-off values for alarm to be personalized for individual patients, acknowledging variation in normal ranges (e.g. accepting lower cut-off values for white cell counts in people of certain ethnic origins).

It should also be emphasized that in the event of new laboratory abnormalities, it is important to consider alternative explanations, especially in patients who have been stable on therapy for prolonged periods. For example, development of macrocytosis in a patient who has been stable on DMARD therapy for an extended period should prompt standard investigations for vitamin B_{12}/folate deficiency, thyroid function and assessment of alcohol consumption.

The guideline makes reference to absolute values for all laboratory abnormalities with the exception of creatinine. The choices of the individual cut-off values for contacting the rheumatology team are based upon what is generally considered a significant deviation from the normal ranges for the test. Normal ranges for absolute values vary across laboratories, and therefore local users will need to bear in mind their own laboratory values.

The GWG felt that the average user of the guidelines would find absolute values easier to use in practice and therefore these were adopted where possible. For situations where there are no established absolute cut-off levels for alarm (albumin or mean cell volume), values of ~2 S.D. from the population mean have been used. Renal function is an exception because the variability in the normal range is much greater and is also dependent upon body mass and age; therefore, an absolute value cut-off is inappropriate.

The guideline includes monitoring of eosinophil counts as historically eosinophilia was an important marker for identifying toxicity from gold therapy. As gold is now infrequently used as a DMARD, eosinophilia is less relevant to monitoring.

As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g. gradual decreases in WBC or albumin, or increasing liver enzymes).

For clinically urgent abnormalities, emergency access to specialist rheumatology advice, with response within one working day, should be available as per NICE guidelines.

Applicability and utility

Clinician responsibility

These guidelines represent a framework upon which clinical practice should be based. However, as with any guideline, individual patient circumstances can have important influences on clinical decision-making. The art of medicine relies upon a clinician working alongside patients to make shared decisions about care. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence.

Potential organizational barriers to the guideline

An important consideration regarding DMARD monitoring is the impact of frequent blood monitoring on health-care services. Effective DMARD monitoring requires systems in place not only to ensure that patients have regular blood tests, but also that the results of tests are reviewed and acted upon appropriately within a timely manner. Across the UK, there are many examples of excellent practice, with a variety of monitoring approaches adopted within primary and secondary care settings.

DMARD initiation should take place only under the supervision of an expert in the management of rheumatic disease; a recommendation supported across the NICE guidelines across the rheumatic disease areas. However, this revised DMARD guideline intentionally does not make any recommendation as to where monitoring should take place, because this will vary according to local demands and facilities.

The guideline has specifically addressed the intensity of monitoring and, where appropriate, recommendations have been relaxed. The result is that the current revision aims to reduce the burden of monitoring upon clinical services without impacting upon quality of care.

The guideline makes two specific recommendations that will increase monitoring burden: recommendation for routine documentation of height and weight prior to DMARD initiation; and recommendation to include objective retinal screening for patients receiving HCQ.

The frequency of laboratory monitoring has changed for a number of DMARDs, with an overall impact to reduce the burden of blood testing.

Audit tool

It is important to acknowledge that although any individual rheumatology department may care for several thousand patients with rheumatic disease on DMARD therapy, a majority of these patients may be receiving monitoring in primary care. In contrast to secondary care units, a primary care practice may have only a small number of patients on DMARD therapy. Therefore, for meaningful audit to be undertaken, audit should take place across primary and secondary care boundaries. It is anticipated that the secondary care rheumatology services will normally take the lead for auditing DMARD monitoring.

A model audit tool template is available for initiation and monitoring. The template is designed for the most common DMARDs used, but could easily be adapted to suit DMARDs with monitoring schedules outside the standard (e.g. MMF or TCL). The audit tool can be accessed on the BSR website.

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