Newcastle, North Tyneside and Northumberland Guidelines for the Monitoring of Immune Modifying Drugs (IMDs) in Stable Adult Patients (excluding post transplantation) in Primary and Secondary Care

Approved on behalf of the:	
North of Tyne Medicines Guidelines and Use Group	15/1/14
North of Tyne Area Prescribing Committee	March 2014
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Organisations signed up to this guideline:	CCGs North of Tyne, Newcastle upon Tyne Hospitals NHS Foundation Trust, Northumbria Healthcare Foundation Trust
Name of originator/author:	Helen Seymour, updated by Sarah Tulip, Dr J Skinner
Target audience:	All clinicians in the Newcastle, North Tyneside and Northumberland areas involved in the management of patients taking IMDs
Consultation Process:	Guideline group was multidisciplinary from all representative organisations
Mandatory/Statutory Standards or Requirements	Standards for Better Health
Training Requirements	No specific training requirements
Distribution	Primary care, secondary care
Implementation	Implementation process in primary care required as appropriate
Monitoring Compliance	Through audit of referrals received in secondary care

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INTRODUCTION

This local guideline has been developed after reviewing the draft North of Tyne IMD guidelines (2010), NHS Clinical Knowledge Summaries, and current national guidelines. The review group brought together clinicians (consultants and specialist nurses) from a wide range of specialties including rheumatology, gastroenterology, immunology, neurology, dermatology, respiratory and renal medicine as well as GPs, and pharmacists. The aim is to provide guidance to clinicians on the routine monitoring required for adults receiving a range of drugs referred to as Immune Modifying Drugs (IMDs) following dose stabilisation by the initiating specialist.

This local guideline is intended for all clinicians in the Newcastle, North Tyneside and Northumberland areas involved in the management of patients taking IMDs for most conditions other than post transplantation. Where there are specific reasons to deviate from these guidelines then this should be with the specific agreement of local clinical governance committees.

This guideline does not give details of the various arrangements regarding which clinician is responsible for monitoring or prescribing the drugs but seeks to standardise monitoring of stable patients across specialities. Within the North of Tyne (NoT) area there are a range of models for ensuring that patients taking these drugs receive routine monitoring (shared care, hospital only care, community based phlebotomy services). This guidance should be used to ensure consistent monitoring parameters regardless of who does the monitoring.

Monitoring should be offered to all people who are likely to benefit, irrespective of race, disability, gender, age, sexual orientation or religion. Information should be provided to patients in an accessible format and consideration should be given to mobility and communication issues, and being aware of sensitive and cultural issues.

The information given for each drug is not inclusive of all prescribing information and potential adverse effects. Please refer to full prescribing data in the SPC or the BNF.

MONITORING REQUIREMENTS

Tables of testing intervals and parameters are given for a range of IMDs in Appendix 1. Details are given on the recommended course of action if results are outside of the normal range. Clinical judgement should be used, taking into account a full knowledge of a patient's clinical condition and the adverse drug reactions associated with the drug in question, when advising that a drug is stopped or dose reduced. Specialist advice should be sought.

VACCINATION

Patients receiving immunosuppressive therapy (which includes azathioprine, 6- mercaptopurine, ciclosporin, leflunomide, methotrexate, mycophenolate, tacrolimus) are more likely to suffer clinically significant infections. In line with national guidance in the 'Green Book' these patients should be offered annual inactivated influenza vaccination. Patients should also be given pneumococcal vaccination with re-immunisation every 5 years as recommended in the 'Green Book'[1,.] For guidance on choice of pneumococcal vaccine see BNF and Green Book.

The use of live vaccines (e.g., MMR, measles, mumps, oral polio, BCG, yellow fever, live oral typhoid, rubella, Fluenz® - live attenuated nasal influenza vaccine, varicella-zoster vaccine) is contra-indicated unless immunosuppressive drugs are stopped at least 6 months beforehand[2,3]. For individuals due to commence immunosuppressive treatments, inactivated vaccines should ideally be administered at least 2 weeks before commencement to ensure a good immune response. In some cases this will not be possible and therefore vaccination may be carried out at any time and re-immunisation considered after treatment is finished and recovery has occurred. If use of live vaccines is necessary administer at least 4 weeks before immunosuppressive therapy is commenced.

The zoster (shingles) vaccine (Zostavax) is a live vaccine which can be given to some patients at 70 years of age as part of the national vaccination programme where patients are eligible as defined in the 'Green Book'[4].
N.B. Therapy with low-doses of methotrexate (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day), or 6mercaptopurine (<1.5 mg/kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, and other conditions are not considered sufficiently immunosuppressive and are not contraindications for administration of zoster vaccine[5]**.** The Green Book further states that more intensive immunosuppression is, however, considered to be a contra-indication to the use of Zostavax and the vaccine should in general be avoided in patients on potent immunosuppressants such as cyclophosphamide and biologic drugs.

CLOSE CONTACTS OF IMMUNOSUPPRESSED INDIVIDUALS

To minimise the risk of infection, close contacts of immunosuppressed individuals should be fully immunised according to the UK schedule, as a matter of priority. Close contacts of severely

[1] Some advocate boosters every 2 years, or antibody checks with booster doses when titres wane, but currently there is no national guidance or local consensus from all specialists to recommend this approach routinely
[2] The BSR/BHPR guideline (2008) recommends immunosuppressive drugs are stopped at least 3 months beforehand
[3] The Newcastle Virology team advised 'live vaccines could be considered from 3 months after stopping treatment where there is good reason to vaccinate between 3 and 6 months post stopping medication. This is supported by CDC guidance (MMWR 2011. Vol 60,no.2)' The justification for this should be clearly documented.
[4] Vaccination may be beneficial in younger patients (age > 50 years), but there are currently issues with respect to supply of the vaccine and uncertainty regarding need for / timing of booster doses.
[5]The Newcastle Virology team advised 'no guidance is currently provided for patients on other low dose immunosuppressive regimes and so the vaccine cannot currently be routinely recommended out with these criteria. If it is not possible to administer zoster vaccine to patients before initiation of therapy, assess the immune status of the recipient on a case-by-case basis to determine the relevant risks and benefits. Otherwise, defer vaccination for at least 6 months after discontinuation of such therapy (making it consistent with recommendations for other vaccines) (CDC – Guide to vaccine contraindications and precautions)'.

immunosuppressed individuals should also be offered inactivated vaccine against influenza (there is the potential for respiratory spread with the live intranasal influenza vaccine which should be avoided). This will reduce the risk of vulnerable individuals being exposed to the serious consequences of vaccine-preventable infections.
It is important to ensure that household contacts are immune to measles. There have been recent outbreaks of measles in the North East. Household contacts who have not received two doses of a measles containing vaccine should be offered MMR vaccine. Varicella vaccination of children within the household who do not have a history of chickenpox should also be considered[6].

CHICKEN POX/SHINGLES/MEASLES EXPOSURE

Ninety percent of adults are already immune and do not require routine testing of immunity against varicella zoster (VZV)[7,8]. (Children starting immunosuppressive therapy should have their VZV immunity checked and immunised as appropriate prior to treatment).

For patients who have significant contact with an individual with either chicken pox or shingles IgG testing should be arranged by contacting your local laboratory. Further advice is also available from Public Health England on 0191 282 1104, who will also organise VZ immunoglobulin (VZIG) if the patient is susceptible (VZV IgG negative). VZIG should be given within 7 days of contact. It is not completely effective and patients should be advised to obtain early treatment should any symptoms develop.

Significant contact as defined in the 'Green Book', is contact with an individual with chickenpox or disseminated shingles from 2 days before rash appearance until lesions are fully crusted, or an individual with localised zoster on an exposed area from the day of rash onset until lesions are fully crusted. Immunocompromised patients with shingles should be considered infectious even if lesions are covered. Contact in the same room (house, classroom, four-bedded bay) for over 15 minutes or face to face contact is considered significant.

There has been an increase of cases of measles recently, with a large outbreak in the North East in 2012/13. If an immunocompromised patient has been in contact with a case of possible measles urgent measles IgG testing should be arranged by contacting your local laboratory. Further advice is available for patients testing IgG negative from the virologists at the Public Health England Laboratory on 0191 282 1104 as prophylaxis with immunoglobulin may be required.

BLOOD BORNE VIRUS TESTING BEFORE STARTING IMMUNOSUPPRESSION

Patients should be tested for blood borne viruses before initiation of immunosuppressive therapy, including for hepatitis B virus, hepatitis C virus and HIV. Other guidance should be referred to and specialist advice obtained in the event of any of the screening tests being positive.

[6] There is a lot of experience and work with MMR and varicella vaccine (both live vaccines), and these are not contraindicated in household contacts of immuno-compromised patients (Green Book). There are no alternative vaccines and the benefits of vaccinating household contacts are considered to outweigh any potential risk.
[7] Prof Judith Breuer, Professor of Virology UCL advised possibly test for VZV IgG if adult patient from Indian subcontinent, Sri Lanka etc, because chickenpox is less common (can be around 40-50% adult seroprevalence) and so a history of chickenpox is less reliable
[8] The Newcastle Virology team advised 'Testing for immunity to varicella and measles prior to immunosuppression, with vaccination of those testing negative is not routinely recommended in adults (although children should be assessed for measles and varicella immunity and vaccinated appropriately). Rationale is that greater than 90% of adult will have immunity and current IgG assays may be negative despite immunity. Vaccine response is likely to be relatively poor in those with chronic illness and protection could not be assumed after vaccination, hence checking of immunity would still be required in the event of any contact.'

INFECTIONS

RA patients have an increased incidence of infection compared with the general population. Increased disease severity, corticosteroid use and comorbidities are associated with an increased infection risk. However it was noted that low-dose methotrexate does not appear to increase infection risk in RA patients[9].
Recurrent confirmed bacterial infections and/or opportunist infection should be flagged as requiring further attention and investigation.
Patients who have a concomitant infection whilst on methotrexate, mycophenolate, leflunomide, ciclosporin or tacrolimus should have their IMD temporarily stopped until the infection has cleared.

PREGNANCY

Patients planning pregnancy should discuss this well in advance with their specialist (including men if they are taking methotrexate (although a recent publication reported no increase in major malformations in children born of men taking methotrexate, the numbers in the study were limited[10]) or leflunomide; sulfasalazine affects sperm count and motility and so may affect ease of conception). Although all IMDs are potentially hazardous in pregnancy, long clinical experience shows that for some agents the magnitude of these risks has been overstated, however methotrexate and leflunomide remain absolutely contraindicated in pregnancy as both these agents are known teratogens and methotrexate is an abortifacient. mycophenolate Mofetil has also been associated with congenital malformations and cases of spontaneous abortions have been reported in patients exposed to mycophenolate mofetil. The benefits of continuing azathioprine or hydroxychloroquine also usually outweigh the risk.

SAFE ALCOHOL LIMITS

Methotrexate and alcohol may both increase the risk of liver damage, but there was no consensus by the group to recommend a lower than the national limit for alcohol consumption in patients who are taking methotrexate. Patients should be advised that there is some uncertainty about what are safe levels, and that they should certainly ensure their consumption is within the recommended maximum limits of 2-3 units per day for women and 3-4 units per day for men with at least 2 alcohol free days per week (i.e. maximum 14 units per week in women, 21 units per week in men). The risk of liver toxicity may be greater in those with psoriasis or psoriatic arthritis than in individuals who have rheumatoid arthritis, but there was no consensus by the group to make different recommendations for those with different inflammatory conditions. The consensus of the group was to make the same recommendations for those taking other potential hepatotoxins such as leflunomide

MONITORING RECORDS

All patients should have a hand held monitoring booklet to record details of results unless a suitable IT monitoring system is in place and accessible to **both** primary and secondary care. A patient information leaflet for methotrexate is available from the NPSA.

CONTACT DETAILS

Further advice is available from a consultant virologist, Health Protection Agency Laboratory, Newcastle upon Tyne. Telephone 0191 2821104

[9] Methotrexate, rheumatoid arthritis and infection risk—what is the evidence? Rheumatology 2009;48:867–871
[10] Viktil, KK et al. Scan J Rheumatol. 2012 41 p196

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Tacrolimus not interchangeable without careful monitoring. MHRA – Drug safety Alert. February 2010.. http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/index.htm

APPENDIX 1. MONITORING REQUIREMENTS FOR INDIVIDUAL DRUGS
AZATHIOPRINE AND 6- MERCAPTOPURINE

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipids	BP	Urinalysis	Other important warnings	Important interactions
Azathioprine/ 6 Mercaptopurine	Once stable (usually after 6 months) every 3 months In people heterozygous for thiopurine methyl transferase (TPMT), monitoring should continue at monthly intervals (TPMT status should be determined in secondary care before starting treatment — azathioprine should not be given to people who are TPMT-homozygote). Treatment dose should be adjusted appropriately in TPMT heterozygotes. [11]	Once stable (usually after 6 months) every 3 months	Once stable (usually after 6 months) every 3 months	RHEUMATOLOGY AND GASTROENTEROLOGY PATIENTS ONLY (marker of disease activity) Following dose stabilisation check at same time as other monitoring tests ie every 3 months	NA	NA	NA	Hypersensitivity reactions (including malaise, dizziness, rigors, myalgias, rashes, fever, abnormal liver function, arrythmias and hypotension)- **STOP** drug. Seek urgent advice. Supportive circulatory measures needed if severe. Rash or oral ulceration – **STOP** drug and seek urgent advice Abnormal bruising or severe sore throat – **STOP** and seek advice Unexplained cough, dyspnoea - **STOP** drug and seek advice	The following drugs should not be started without discussion with the initiating specialist **ALLOPURINOL** - risk of severe myelosuppression : **WARFARIN** - effect may be reduced requiring increased dose of warfarin **TRIMETHOPRIM or CO-TRIMOXAZOLE** - potential risk of haematological toxicity **AMINOSALICYLIC ACID DERIVATIVES e.g. OLSALAZINE, MESALAZINE AND SULPHASALAZINE** - risk of an increased myelosuppressive effect **RIBAVIRAN –** possibly enhances myelosuppressive effects of azathioprine **REBUXOSTAT –** avoid concomitant use with azathioprine
	Neutropenia <2.0 x 10^9/L Sequential falls in WBC or neutrophils >10% on 3 occasions Thrombocytopenia <150 x 10^9/L — **STOP** and seek advice Sequential falls in platelets - **STOP** unless falls are from high level Lymphocytes <0.5 x 10^9/L - Seek advice Macrocytosis >105 fl Check B12 and folate, thyroid function have been checked within last 12 months and are normal		Elevation of ALT >2 x upper limit of reference range - seek advice; >3 upper limit of reference range - **STOP**. Repeat LFTs. Mild transaminitis is common and normally settles						

[11] Dr Bridget Griffiths advised that at NuTH they give a lower maximum dose i.e. 1.5 mg/kg instead of 2.5 mg/kg but all patients receive their monitoring at the same frequency

CICLOSPORIN

NB There are various brands of ciclosporin – these are NOT interchangeable – prescribe by brand name.

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipids	BP	Other important warnings	Important interactions
Ciclosporin	Every 2 weeks until dose stable for three months, then ONCE a month	Every 2 weeks until dose stable for three months, then ONCE a month	Every 2 weeks until dose stable for three months, then ONCE a month	RHEUMATOLOGY PATIENTS ONLY (marker of disease activity) Following dose stabilisation check at same time as other monitoring tests ie every month	Every 6 months	Every 2 weeks until dose stable for three months, then monthly	Unexplained cough, dyspnoea, abnormal bruising or bleeding - **STOP** drug and seek advice **Ciclosporin levels** – trough drug levels may be indicated/considered if there are concerns about toxicity or concordance	The following drugs should not be started without discussion with the initiating specialist: **ACE INHIBITORS & ARIIAs**: increased risk of hyperkalaemia **ANTIBIOTICS**: erythromycin, azithromycin and clarithromycin increase ciclosporin levels; rifampicin decrease ciclosporin levels **ANTIFUNGALS**: fluconazole, itraconazole, and ketoconazole decrease ciclosporin levels **CALCIUM-CHANNEL BLOCKERS**: diltiazem, nicardipine and verapamil increase ciclosporin levels **ANTIEPILEPTICS**: carbamazepine, phenobarbital, and phenytoin decrease ciclosporin levels **ANTI-MALARIAL DRUGS**: Hydroxycholoquine and chloroquine increase ciclosporin levels **ANTI-OBESITY DRUGS**: orlistat decreases ciclosporin levels **NSAIDs** (and other nephrotoxic drugs): increased risk of nephrotoxicity **STATINS**: lower doses should be used to reduce risk of muscular toxicity, however there is still a risk of myopathy with lowered doses. Avoid simvastatin and rosuvastatin is contraindicated with ciclosporin **POTASSIUM_ SPARING DIURETICS**: only initiate with regular monitoring of U&Es **HERBAL MEDICINES**: Avoid **GRAPEFRUIT JUICE**: Avoid as increases ciclosporin levels **NUMEROUS OTHERS**: check BNF for details
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 10^9/L Sequential falls in WBC neutrophils >10% on 3 occasions Thrombocytopenia <150 x 10^9/L **STOP** and seek advice Sequential falls in platelets - **STOP** unless falls are from high level Lymphocytes <0.5 x 10^9/L - Seek advice Macrocytosis >105 fl Check B12 and folate, thyroid function have been checked within last 12 months and are normal	Increase in creatinine - >30% from baseline – reduce dose by 50% - >50 % above baseline – **STOP** drug and seek advice	Elevation of ALT >3 x upper limit of reference range - **STOP**. Repeat LFTs. Mild transaminitis is common and normally settles		Significant rise in fasting lipids **STOP** and seek advice	BP >140/90 on 2 readings 2 weeks apart Treat BP before stopping drug (eg with amlodipine). If uncontrolled **STOP** and control BP before restarting ciclosporin. Seek advice		

HYDROXYCHLOROQUINE

Drug	Eye checks	Important interactions
Hydroxychloroquine	Ask patients about visual symptoms annually Monitor near visual acuity for each eye annually, using a standard near vision type test wearing reading glasses if worn. If the test is carried out by an optometrist this is at the patient's expense unless they are exempt from charges for other reasons (eg glaucoma). If any visual defect or eye disease is detected at baseline or changes in acuity/blurred vision while on treatment then patients should be advised to consult an optometrist in the first instance. Refer to an ophthalmologist if a patient: - Has visual defect or eye disease is detected at baseline - Notices reduced vision (particularly for reading), patchy central vision or distorted central vision while on treatment. Patients should be warned to seek advice from the prescriber and to have their vision checked by an optometrist. Subsequent examinations should be at the discretion of the ophthalmologist and indefinite follow up is not likely for most patients. If long term treatment is required (more than 5 years) individual arrangements should be agreed with local ophthalmologist.	**Amiodarone** - increased risk of ventricular arrythmias **Moxifloxacin** - increased risk of ventricular arrythmias **Antimalarials –** arthemether/lumefantrine, mefloquine **Droperidol -** increased risk of ventricular arrythmias **Digoxin** – increased digoxin levels **Ciclosporin –** increased ciclosporin levels (increased risk of toxicity) **Mefloquine -** increased risk of convulsions

LEFLUNOMIDE

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipids	BP	Urinalysis	Weight	Other important warnings	Important interactions
Leflunomide **Contraindicated in hypoproteinaemia or impairment of liver function**	Following stabilization every TWO months	Following stabilization every TWO months	Following stabilization every TWO months	RHEUMATOLOGY PATIENTS ONLY (marker of disease activity) Following stabilization every TWO months	NA	Following stabilization every TWO months	NA	Every TWO months	Unexplained cough, dyspnoea, severe rash, excessive weight loss, severe or persistent GI upset, severe, persistent headache, abnormal bruising or severe sore throat, severe hair loss - **STOP** drug and seek advice – **WASHOUT** procedure may be required due to the long half life of the drug – see below for details	**Cholestyramine** - dramatically increases elimination (may be used if **WASHOUT** required – see below for details). Care with **phenytoin**, **warfarin** and **tolbutamide** **METHOTREXATE –** increased risk of toxicity.
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 10^9/L **STOP** Sequential falls in WBC or neutrophils >10% on 3 occasions and seek advice Thrombocytopenia <150 x 10^9/L Sequential falls in platelets - **STOP** unless falls are from high level Lymphocytes <0.5 x 10^9/L - Seek advice Macrocytosis >105 fl Check B12 and folate, thyroid function have been checked within last 12 months and are normal		Elevation of ALT>2 x upper limit of reference range - seek advice Elevation of ALT >3 x upper limit of reference range - **STOP**. Repeat LFTs. Mild transaminitis is common and normally settles. Repeat LFTs. Early sign of liver toxicity			>140/90 Mild rises seen in 10% of patients. Reduce dose if marked increase. Consider anti-hypertensives. **STOP** drug if refractory to these measures.		If > 10% weight loss with no other cause identified – seek advice		

WASHOUT procedure (BNF 58): To aid drug elimination in case of serious adverse event, or before starting another IMD, or before conception (but see introduction section on preconception advice) – STOP treatment and give either colestyramine 8g three times daily for 11 days or activated charcoal 50g four times daily for 11 days; the concentration of active metabolite should be less than 20 micrograms/litre (measured on 2 occasions 14 days apart) in men and women before conception – consult product literature. Procedure may be repeated as necessary.

METHOTREXATE

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipids	BP	Urinalysis	Other important warnings	Important interactions
Methotrexate Baseline chest Xray and pulmonary function tests **NB** Prescribe folic acid 5mg/ calcium folinate 15mg ONCE a week (usually 3 - 4 days after the methotrexate dose)	Monthly for first year and then every 2 months.* For some specialties (e.g., Dermatology) testing every 3 months may be acceptable	Monthly for first year and then every 2 months. For some specialties (e.g., Dermatology) testing every 3 months may be acceptable	Monthly for first year and then every 2 months. For some specialties (e.g., Dermatology) testing every 3 months may be acceptable	RHEUMATOLOGY AND GASTROENTEROLOGY PATIENTS ONLY (marker of disease activity) Following dose stabilisation check at same time as other monitoring tests	NA	NA	NA	Unexplained cough, dyspnoea, rash, severe, oral ulceration, severe nausea/vomiting/ diarrhoea, abnormal bruising or bleeding , or severe sore throat, - **STOP** drug and seek advice Advise patients to stay well within the national recommendations for alcohol intake	Numerous - check BNF; important ones include **ANTIBIOTICS** - avoid trimethoprim and co-trimoxazole **Phenytoin** - antifolate effect of methotrexate increased by phenytoin **Retinoids** - plasma concentration of methotrexate increased by acitretin (also increased risk of hepatotoxicity) **NSAIDs** are routinely co-prescribed for inflammatory arthritis (although they elevate serum levels) - adherence to monitoring schedule is advised. **HERBAL PREPARATIONS** - may increase risk of toxicity and include Echinacea, Bishop's weed, Kava, Black cohosh and Borage **Probenecid** - increased risk of toxicity **Clozapine** - **Avoid concomitant use** increased risk of agranulocytosis LEFLUNOMIDE – increased risk of toxicity. Increased monitoring vigilance advised when used in combination.
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 10^9/L **STOP** Sequential falls in WBC or neutrophils >10% on 3 occasions and seek advice Thrombocytopenia <150 x 10^9/L Sequential falls in platelets - **STOP** unless falls are from high level Lymphocytes <0.5 x 10^9/L - Seek advice Macrocytosis >105 fl Check B12 and folate, thyroid function have been checked within last 12 months and are normal	Worsening renal function should be discussed with the specialist – Methotrexate is renally excreted and any reduction in renal function (e.g. as a consequence dehydration or coprescription of diuretics/ACEIs) may cause serious toxicity	Elevation of ALT >2 x upper limit of reference range - seek advice; >3 x upper limit of reference range - **STOP**. Repeat LFTs. Mild transaminitis is common and normally settles. Albumin- unexplained fall (in absence of active disease) - Withhold until discussed with specialist team						

The information given for this drug is not inclusive of all prescribing information and potential adverse effects. Please refer to full prescribing data in the SPC or the BNF.

MINOCYCLINE

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipids	BP	Urinalysis	Other important warnings	Important interactions
Minocycline (unlicensed as a disease modifying anti-rheumatic drug) **Patients will be screened pretreatment for presence of ANA autoantibodies : a significant titre of these will be taken as a relative contraindicatio n to minocycline treatment.**	Monthly for first three months and thereafter three monthly	Monthly for first three months and thereafter three monthly	Monthly for first three months and thereafter three monthly	RHEUMATOLOGY PATIENTS ONLY (marker of disease activity) Following dose stabilisation check at same time as other monitoring tests	NA	NA	NA	Rare cases of auto-immune hepatotoxicity and isolated cases of SLE and also exacerbation of pre-existing SLE have been reported. If patients develop signs or symptoms of SLE or hepatotoxicity minocycline should be discontinued. Advise patients to stay well within the national recommendations for alcohol intake Patients should be advised to report any unusual pigmentation without delay - seek advice	**Warfarin** - possibly enhance anticoagulant effect **Retinoids** - possible increased risk of benign intracranial hypertension when tetracyclines given with retinoids (avoid concomitant use)
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 10^9/L **STOP** Sequential falls in WBC or neutrophils >10% on 3 occasions and seek advice Thrombocytopenia <150 x 10^9/L Sequential falls in platelets - **STOP** unless falls are from high level Lymphocytes <0.5 x 10^9/L - Seek advice		Elevation of ALT >2 x upper limit of reference range - seek advice; >3 x upper limit of reference range - **STOP**.						

MYCOPHENOLATE

NB There are various brands of mycophenolate – these are NOT interchangeable – prescribe by brand name.

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipids	BP	Urinalysis	Other important warnings	Important interactions
Mycophenolate	Following stabilisation monitor ONCE a month	Following stabilisation monitor ONCE a month	Following stabilisation monitor ONCE a month	RHEUMATOLOGY PATIENTS ONLY (marker of disease activity) Following dose stabilisation check at same time as other monitoring tests ie every month	NA	Following stabilisation monitor ONCE a month	Following stabilisation monitor ONCE a month	Unexplained cough, dyspnoea, abnormal bruising or bleeding,severe sore thoat - **STOP** drug and seek advice	**Rifampicin** Reduces levels of active metabolite of mycophenolate **Antacids** may reduce absorption of mycophenolate **Cholestyramine** may reduce absorption and bioavailabilty of mycophenolate by 40% . **Probenecid** increases plasma concentration of mycophenolate. **Aciclovir** causes significant increase in plasma concentration of mycophenolate in patients who have renal impairment
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 10^9/L Sequential falls in WBC or neutrophils >10% on 3 occasions Thrombocytopenia <150 x 10^9/L — **STOP** and seek advice Sequential falls in platelets - **STOP** unless falls are from high level Lymphocytes <0.5 x 10^9/L - Seek advice Macrocytosis >105 fl Check B12 and folate, thyroid function have been checked within last 12 months and are normal	Increase in creatinine - > 140 micromol. STOP, repeat U&Es and seek advice	Elevation of ALT >2 x upper limit of reference range - seek advice; >3 x upper limit of reference range - **STOP**. Repeat LFTs. Mild transaminitis is common and normally settles.				**Haematuria** - Trace or + - Check MSU. Continue drug. ++ or +++ check ACR and seek advice. If evidence of symptomatic UTI check MSU and treat as appropriate. **Proteinuria** - Trace or + - Check MSU. Continue drug. ++ or +++ check albumin/creatinine Ratios (ACR) and seek advice. If evidence of symptomatic UTI check MSU and treat as appropriate		

PENICILLAMINE

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipids	BP	Urinalysis	Other important warnings	Important interactions
Penicillamine	Following stabilisation ONCE a month. For certain patients who have received the drug for a long period it may be possible to reduce the frequency of monitoring to every THREE months at the discretion of the specialist.	Following stabilisation ONCE a month. For certain patients who have received the drug for a long period it may be possible to reduce the frequency of monitoring to every THREE months at the discretion of the specialist.	NA	RHEUMATOLOGY PATIENTS ONLY (marker of disease activity) Following dose stabilisation check at same time as other monitoring tests	NA	NA	Following stabilisation ONCE a month. For certain patients who have received the drug for a long period it may be possible to reduce the frequency of monitoring to every THREE months at the discretion of the specialist.	Unexplained cough, dyspnoea, abnormal bruising or bleeding, severe sore throat - **STOP** drug and seek advice Severe rash or oral ulceration. Late rashes are more serious than early ones - **STOP** drug and seek advice There is a risk of risk of prolonged/permanent hypogammaglobulinaemia	Avoid use of **clozapine** - increased risk of agranulocytosis
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 109/L **STOP** Sequential falls in WBC or neutrophils >10% on 3 occasions and seek advice Thrombocytopenia <150 x 10^9/L Sequential falls in platelets - **STOP** unless falls are from high level Lymphocytes <0.5 x 10^9/L - Seek advice						**Haematuria** - Trace or + - Check MSU. Continue drug. ++ or +++ check ACR and seek advice. If evidence of symptomatic UTI check MSU and treat as appropriate. **Proteinuria** - Trace or + - Check MSU. Continue drug. ++ or +++ check albumin/creatinine Ratios (ACR) and seek advice. If evidence of symptomatic UTI check MSU and treat as appropriate		

SODIUM AUROTHIOMALATE (I.M. GOLD INJECTION)

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipids	BP	Urinalysis	Other important warnings	Important interactions
Sodium aurothiomalate	At each injection	Every 3 months	Every 3 months	RHEUMATOLOGY PATIENTS ONLY (marker of disease activity) At each injection - ESR; 3 monthly - CRP	NA	NA	At each injection	Severe rash, severe mouth ulcers, unexplained cough, dyspnoea, abnormal bruising or bleeding, severe sore throat, nitroid reaction (dizziness, nausea, vomiting, sweating, flushing, hypotension), visual disturbances, severe alopecia, severe diarrhoea - **STOP** drug and seek advice There is a risk of risk of prolonged/permanent hypogammaglobulinaemia	Increased toxicity with other **myelotoxic** and **nephrotoxic** drugs. ACEIs – increased risk of nitroid reactions
	Leucopenia <3.5 x 109/L Neutropenia <2.0 x 109/L Sequential falls in WBC or neutrophils >10% on 3 occasions Thrombocytopenia <150 x 109/L — STOP and seek advice Sequential falls in platelets - STOP unless falls are from high level Macrocytosis >105 fl Check B12 and folate, thyroid function have been checked within last 12 months and are normal Sequential falls in platelets **STOP** unless falls are from high level Eosinophilia – rising trend – reduce dose; advance warning of likely adverse reaction – watch carefully Lymphocytes <0.5 x 10^9/L Seek advice Macrocytosis - >105 fl – check B12 and folate		Elevation of ALT >3x upper limit of reference range – STOP and seek advice. Consider other causes. Rare late side effect. Fall in albumin >5g/L - seek advice; <25g/L – STOP, dipstick urine and send for albumin/creatinine ratio. May be an indication of renal damage (see recommendations for urinalyisis)				**Haematuria** - Trace or + - Check MSU. Continue drug. ++ or +++ check ACR and seek advice. If evidence of symptomatic UTI check MSU and treat as appropriate. **Proteinuria** - Trace or + - Check MSU. Continue drug. ++ or +++ check albumin/creatinine Ratios (ACR) and seek advice. If evidence of symptomatic UTI check MSU and treat as appropriate.		

SULFASALAZINE E.C.

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipids	BP	Urinalysis	Other important warnings	Important interactions
Sulfasalazine E.C.	Once stable monitor every 3 months for 2 years then stop.	Once stable monitor every 3 months for 2 years then stop.	Once stable monitor every 3 months for 2 years then stop.	RHEUMATOLOGY PATIENTS ONLY (marker of disease activity) Following dose stabilisation check at same time as other monitoring tests	NA	NA	NA	Unexplained cough, dyspnoea, abnormal bruising or bleeding, severe sore throat,, severe nausea/ dizziness/ headache , unexplained acute, widespread rash, oral ulceration - **STOP** drug and seek advice	
	Leucopenia <3.5 x 109/L Neutropenia <2.0 x 109/L STOP and seek advice Sequential falls in WBC or neutrophils >10% on 3 occasions Thrombocytopenia <150 x 109/L Sequential falls in platelets - STOP unless falls are from high level Sequential falls in platelets STOP unless falls are from high level Lymphocytes <0.5 x 109/L Seek advice Macrocytosis - >105 fl – check B12 and folate, , thyroid function have been checked within last 12 months and are normal		Elevation of ALT >2 x upper limit of reference range - seek advice; >3 x upper limit of reference range - **STOP**. Repeat LFTs. Mild transaminitis is common and normally settles.						

TACROLIMUS

NB There are various brands of tacrolimus – these are NOT interchangeable – prescribe by brand name.

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipids	BP	Urinalysis	Other important warnings	Important interactions
Tacrolimus	Following stabilisation monitor ONCE a month	Following stabilisation monitor ONCE a month	Following stabilisation monitor ONCE a month	RHEUMATOLOGY PATIENTS ONLY (marker of disease activity) Following dose stabilisation check at same time as other monitoring tests ie every month	Every 6 months	Following stabilisation monitor ONCE a month	NA	Unexplained cough, dyspnoea, abnormal bruising or bleeding - **STOP** drug and seek advice **Tacrolimus levels** – trough drug levels may be indicated/considered if there are concerns about toxicity or concordance	**ANALGESICS** – possible increased nephrotoxicity with NSAIDS and especially **Ibuprofen** **ANTIBACTERIALS –** increased levels with clarithromycin, erythromycin, chloramphenicol and quinupristin/dalfopristin; reduced levels with rifampicin; increased nephrotxicity with aminoglycosides, vancomycin **ANTIDEPRESSANTS –** Increased levels with St Johns Wort **ANTEPILEPTICS** - carbamazepine phenobarbital and phenytoin decrease tacrolimus level, **ANTIFUNGALS –** Increased levels with fluconazole, itraconazole, ketoconazole and voriconazole **AMPHOTERICIN** - increased risk of nephrotoxicity with **ANTIPSYCHOTICS –** Droperidol **ANTIVIRALS –** Increased risk of nephrotoxicity with aciclovir, ganciclovir; **CALCIUM CHANNEL BLOCKERS** _ increased levels with felodipine, nicardipine, verampimil, diltiazem and nifedipine **CICLOSOPRIN –** Increased CyCA levels **DABIGATRAN** - tacrolimus possibly increases plasma concentration of dabigatran avoid concomitant use **DIURETICS and K SALTS– increased risk of hyperkalaemia** **GRAPEFRUIT JUICE –** increased levels
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 10^9/L Sequential falls in WBC or neutrophils >10% on 3 occasions Thrombocytopenia <150 x 10^9/L STOP and seek advice Sequential falls in platelets - STOP unless falls are from high level Lymphocytes <0.5 x 10^9/L - Seek advice Macrocytosis >105 fl Check B12 and folate, thyroid function have been checked within last 12 months and are normal	Increase in creatinine – 30% from baseline – reduce dose by 50% - >50% from baseline – **STOP** drug and seek advice	Elevation of ALT >2 x upper limit of reference range - seek advice; >3 x upper limit of reference range - **STOP**. Repeat LFTs. Mild transaminitis is common and normally settles.		Significant rise in fasting lipids – **STOP** and seek advice	BP> 140/90 on 2 readings 2 weeks apart – treat BP before stopping drug (eg with amlodipine). If uncontrolled **STOP** and control BP before restarting tacrolimus – seek advice			

The information given for this drug is not inclusive of all prescribing information and potential adverse effects. Please refer to full prescribing data in the SPC or the BNF.

APPENDIX 2 - MEMBERSHIP OF THE GUIDELINE GROUP

Dr JS Skinner	Consultant Community Cardiologist / Clinical Director for Community Services	The Newcastle upon Tyne Hospitals NHS FT (guideline lead)
Dr S Bourke	Consultant Respiratory Physician	The Newcastle upon Tyne Hospitals NHS FT
Dr S Bourke	Consultant Respiratory Physician	Northumbria Healthcare NHS FT
Mr I Campbell	Assistant Director of Pharmacy	The Newcastle upon Tyne Hospitals NHS FT
Dr A De Soyza	Consultant Respiratory Physician	The Newcastle upon Tyne Hospitals NHS FT
Dr I Forrest	Consultant Respiratory Physician	The Newcastle upon Tyne Hospitals NHS FT
Dr B Griffiths	Consultant Rheumatologist	The Newcastle upon Tyne Hospitals NHS FT
Dr M Grove	Consultant Rheumatologist	Northumbria Healthcare NHS FT
Dr M Hudson	Consultant Hepatologist	The Newcastle upon Tyne Hospitals NHS FT
Dr M Jackson	Consultant Neurologist	The Newcastle upon Tyne Hospitals NHS FT
Dr L Kay	Consultant Rheumatologist	The Newcastle upon Tyne Hospitals NHS FT
Dr S Leech	Consultant Dermatologist	The Newcastle upon Tyne Hospitals NHS FT
Dr J Lordan	Consultant Respiratory Physician	The Newcastle upon Tyne Hospitals NHS FT
Dr J Mansfield	Consultant Gastroenterologist	The Newcastle upon Tyne Hospitals NHS FT
Dr J Matthews	GP	North Tyneside
Dr J McClelland	Consultant Dermatologist	The Newcastle upon Tyne Hospitals NHS FT
Dr S Meggitt	Consultant Dermatologist	The Newcastle upon Tyne Hospitals NHS FT
Dr J Miller	Consultant Neurologist	The Newcastle upon Tyne Hospitals NHS FT
Ms J Murphy	Lower Gastroenterology Nurse Specialist	Northumbria Healthcare NHS FT
Dr E Phillips	Consultant Gastroenterologist	Northumbria Healthcare NHS FT
Ms A Rodway	Chronic Disease Monitoring Lead	The Newcastle upon Tyne Hospitals NHS FT
Mr M Scott	GP	Newcastle upon Tyne
Mrs HE Seymour	Senior Medicines Management Adviser	NHS
Dr D Shovlin	GP	Northumberland
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Dr J Tapson	Consultant Nephrologist	The Newcastle upon Tyne Hospitals NHS FT
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Declared conflicts of interest
None declared

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