NHS North of Tyne

Clinical Guidelines

Guideline Number: NoT 20

Newcastle, North Tyneside and Northumberland Guidelines on Monitoring Immune Modifying Drugs in Stable Adult Patients

Ratified by:	NHS North of Tyne Commissioning Integrated Governance Committee
Date ratified:	July 2010
Date issued:	November 2010
Review date:	July 2013
Organisations signed up to this guideline:	NHS North of Tyne (on behalf of the PCT's), Newcastle upon Tyne Hospitals NHS Foundation Trust, Northumbria Healthcare Foundation Trust
Name of originator/author:	Helen Seymour
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. Distributed to GPs and uploaded onto infonet.
Monitoring Compliance	Through audit of referrals received in secondary care

NHS North of Tyne

Clinical Guidelines

Guideline Number: NoT 20

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

Ratified by:	NHS North of Tyne Commissioning Integrated Governance Committee
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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 DMARD guidelines (2004), 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 organ 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 influenza vaccination. Patients should also be given pneumococcal vaccination with re-immunisation every 5 years.

The use of live vaccines (e.g., MMR, BCG, yellow fever, live oral typhoid, rubella) is contra-indicated unless immunosuppressive drugs are stopped at least 3 months beforehand. If use of live vaccines is necessary allow at least 2 weeks, preferably 4 weeks before immunosuppressive therapy is commenced.

CHICKEN POX/SHINGLES EXPOSURE[1]

Ninety percent of adults are already immune and do not require routine testing of immunity against varicellar zoster (VZV). (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 then IgG testing should be arranged by contacting your local laboratory. Further advice is also available from the Health Protection Agency (HPA) laboratory on 0191 226 1074, 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 shingles 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.

PREGNANCY

Patients planning pregnancy should discuss this well in advance with their specialist (including men if they are taking methotrexate and leflunomide; sulfasalazine affects sperm 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 abortifacient.

[1] Personal communication, Dr Sheila Waugh, Consultant Virologist, The Newcastle upon Tyne Hospitals NHS Trust

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 (ie 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

Health Protection Agency Laboratory, Newcastle upon Tyne	0191 226 1074
Dr S Waugh, Consultant Virologist	0191 244 8948

REFERENCES

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APPENDIX 1. MONITORING REQUIREMENTS FOR INDIVIDUAL DRUGS

AZATHIOPRINE AND 6- MERCAPTOPURINE

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipds	BP	Urinalysis	Other important warnings	Important interactions
Azathioprine/ 6 Mercaptopurine	Once stable (usually after 6 months) every 3 months	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. Unexplained cough, dyspnoea, abnormal bruising or bleeding - **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 abnormalities
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 10^9/L **STOP** Sequential falls in WBC and or neutrophils >10% seek on 3 occasions 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; >3 upper limit of reference range - **STOP**. Repeat LFTs. Mild transaminitis is common and normally settles Fall in albumin >5g/L - seek advice; <25g/L - **STOP**. Repeat LFTs. Early sign of liver toxicity						

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 lipds	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 and clarithromycin increase ciclosporin levels; rifampicin decrease ciclosporin levels **ANTIFUNGALS**: fluconazole, itraconazole, and ketoconazole increase 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): should be used with caution **STATINS**: lower doses should be used to reduce risk of muscular toxicity, however there is still a risk of myopathy with lowered doses **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 or 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	An annual near visual acuity check on each eye. This can be performed for each eye 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. It is appropriate to refer to an ophthalmologist if a patient 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.	**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 cycA levels

LEFLUNOMIDE

Drug	FBC	U&Es/ serum creatinine	LFTs	ESR/CRP	Serum lipds	BP	Urinalysis	Other important warnings	Important interactions
Leflunomide	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	Unexplained cough, dyspnoea, severe rash, excessive weight 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**
	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. Fall in albumin >5g/L - seek advice Albumin <25g/L - **STOP**			>140/90 Mild rises seen in 10% of patients. Reduce dose if marked increase. Consider anti-hypertensives. **STOP** drug if refractory to these measures.			

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 3 times daily for 11 days or activated charcoal 50g 4 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 lipds	BP	Urinalysis	Other important warnings	Important interactions
Methotrexate **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, abnormal bruising or bleeding - **STOP** drug and seek advice	Numerous - check BNF; important ones include : **ANTIBIOTICS** - avoid trimethoprim and co-trimoxazole **Phenytoin** **Retinoids** **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
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 10^9/L **STOP** Sequential falls in WBC and or neutrophils >10% seek on 3 occasions 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 of 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. Fall in albumin >5g/L - seek advice; <25g/L - **STOP**. Repeat LFTs. Early sign of liver toxicity						

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 lipds	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 - **STOP** drug and seek advice	**ANTIBACTERIALS**: Rifampicin Increases levels
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 10^9/L **STOP** and Sequential falls in WBC or neutrophils >10% on 3 occasions 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	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. Fall in albumin >5g/L - seek advice; <25g/L - **STOP**. Repeat LFTs. Early sign of liver toxicity				**Haematuria** - Trace or + - Check MSU. Continue drug. - ++ or +++ - **STOP** drug. Check MSU. Consider other causes. Seek advice **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 lipds	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 - **STOP** drug and seek advice	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 +++ - **STOP** drug. Check MSU. Consider other causes. Seek advice **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 lipds	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, nitroid reaction (flushing, hypotension), visual disturbances, severe alopecia, severe diarrhoea - **STOP** drug and seek advice	Increased toxicity with other **myelotoxic** and **nephrotoxic** drugs. ACEIs – increased risk of nitroid reactions
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 10^9/L **STOP** Sequential falls in WBC and or neutrophils >10% seek on 3 occasions advice Thrombocytopenia <150 x 10^9/L } 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**. Repeat LFTs. Early sign of liver toxicity				**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 lipds	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 - **STOP** drug and seek advice	
	Leucopenia <3.5 x 10^9/L Neutropenia <2.0 x 10^9/L **STOP** Sequential falls in WBC and or neutrophils >10% seek on 3 occasions 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; >3 x upper limit of reference range - **STOP**. Repeat LFTs. Mild transaminitis is common and normally settles. Fall in albumin >5g/L - seek advice; <25g/L - **STOP**. Repeat LFTs. Early sign of liver toxicity						

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 lipds	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	**NUMEROUS –** consult BNF **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 **ANTIFUNGALS –** Increased levels with fluconazole, itraconazole, ketoconazole and voriconazole **ANTIPSYCHOTICS –** Droperidol **ANTIVIRALS –** Increased risk of nephrotoxicity with acyclovir, ganciclovir; **CALCIUM CHANNEL BLOCKERS** _ increased levels with felodipine, nicardipine, verampimil, diltiazem and nifedipine **CICLOSOPRIN –** Increased CyCA levels **DIURETICS and K SALTS–** increased K levels with K-sparing diuretics and aldosterone antagonists **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. Fall in albumin >5g/L - seek advice; <25g/L - **STOP**. Repeat LFTs. Early sign of liver toxicity		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			

APPENDIX 2

MEMBERSHIP OF THE GUIDELINE GROUP

Dr JS Skinner	Consultant Community Cardiologist	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
Mr T Dunkerton	Head of Planned Care	NHS North of Tyne
Dr I Forrest	Consultant Respiratory Physician	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
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Dr L Kay	Consultant Rheumatologist	The Newcastle upon Tyne Hospitals NHS FT
Dr S Leech	Consultant Dermatologist	The Newcastle upon Tyne Hospitals NHS FT
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Dr J Mansfield	Consultant Gastroenterologist	The Newcastle upon Tyne Hospitals NHS FT
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Dr S Meggitt	Consultant Dermatologist	The Newcastle upon Tyne Hospitals NHS FT
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Declared conflicts of interest
None declared

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