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Immunosuppresant drugs for the Management of Inflammatory Dermatological conditions

November 2015

This guideline has been subject to consultation with Barnsley Consultant Dermatologists Dr N Hardcastle and Dr K Baxter. The guidance was initially drafted in October 2015 by Gillian Turrell (Lead Pharmacist, BHNFT) and aims to support the consolidation of an effective and patient-specific shared care agreement between the secondary care specialist and primary care GP

This guideline has been subject to consultation and endorsement by:

- *The Area Prescribing Committee on **11th November 2015***
- *The LMC on **14th June 2016***

Background Information

Azathioprine, methotrexate, mycophenolate and ciclosporin are well established as second line drugs in treating a range of inflammatory skin conditions. General Practitioners (GPs) are becoming more involved in active management of these conditions with the recognition that patients should be referred early for specialist advice and initiation.

Please note that the skin conditions which these drugs are used are detailed in each of the drug monographs below. Where used for **unlicensed indications** their use has strong peer group support amongst Dermatologists, and as such is routinely recommended in national treatment guidelines.

Azathioprine, methotrexate, mycophenolate and ciclosporin are immunosuppressant agents and should be initiated in secondary care. Once patients are stabilised on their treatment it is feasible for the ongoing prescribing and monitoring to be undertaken in primary care, with review in secondary care when appropriate. Due to the relatively toxic nature of these drugs it is vital that the ongoing prescribing and monitoring is agreed between the specialists in secondary care and the patient's GP.

Procedure for Initiating Shared Care Arrangements

It is optional for GPs to participate in taking on responsibility for shared care for the patient. GPs will take on shared care only if they are willing and able. In cases where shared care arrangements are not in place, or where problems have arisen with the agreement such that patient care may suffer, the responsibility for the prescribing and management of the patient will revert to the secondary care provider/specialist. Sharing of care assumes communication between the specialist, GP and patient and/or patient's carers. The intention to share care should be explained to the patient/carer and accepted by them.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use. They are responsible for ensuring blood tests are being performed and the results are recorded in the patients monitoring and dosage record.

Patients should be stabilised in secondary care prior to referral to primary care management

Responsibilities of the specialist initiating treatment

Summary

- Diagnosis and assessment
- Initiation and stabilisation of drug therapy (this will usually take a period of 3 months for azathioprine, up to 6 months for methotrexate and ciclosporin and 12 months for mycophenolate)
- Check for any drug interactions when initiating treatment
- Notify the patient's GP that treatment has commenced (See Appendix B for a copy of the letter and Appendix C for a summary of information)
- Baseline monitoring followed by monitoring until the patient is stabilised
- Ensure patient is fully informed of potential benefits and side effects of treatment
- Ensure patient's guardian/carer is fully informed of the treatment
- Provide a comprehensive treatment package in addition to medications including appropriate information/monitoring sheet(s)
- Ensure that shared care arrangements are in place before transfer of treatment
    - That the GP has been contacted with a request they take over prescribing
    - The patient's GP has been notified of the results of the baseline tests.
    - That the patient/carer is clear what is being monitored and by whom
    - That the patient knows what significant adverse effects/events to report urgently and to whom they should report (specialist or GP)
- Any dose changes once the patient is established on treatment will be conveyed in writing to the GP for the GP to prescribe
- Extra monitoring needed for dose changes will be organised by Dermatology team and conveyed to the patient
- Monitor side effects of medication via routine out-patient visits
- Report adverse events to the CSM/MHRA via the yellow card system.
- Monitor patient's response to treatment

Responsibilities of other prescribers

Acceptance of Responsibility by the Primary Care Clinician

It is optional for GPs to participate in taking on responsibility for shared care for the patient. GPs will take on shared care only if they are willing and able.

Summary

- When the specialist initiates treatment, **reply to the request for shared care as soon as practicable**
- Ensure that shared care arrangements are in place before transfer of treatment
- That the patient/carer is clear what is being monitored and by whom
- That the patient knows what significant adverse effects/events to report urgently and to whom they should report (specialist or GP)
- Confirm that proposed therapy is not contra-indicated because of concurrent therapy for other conditions the patient may be suffering from e.g. check drug-contraindications and drug-interactions. Contact specialist team if possible interactions found and discuss with dermatologist
- Confirm the specialists have provided the patient/carer with appropriate information sheet(s) for monitoring and/or to alert other clinical staff to the treatment they are receiving. If appropriate information has not been provided by the specialist, the GP must ensure the information is provided
- Ensure patient's guardian/carer is fully informed of the treatment
- Monitor treatment as stated in the shared care protocol
- Amend prescription as per requests from secondary care for dose changes in patients on established treatment
- Confirm with specialist which changes should trigger urgent referral back to the specialist
- Seek specialist advice promptly as advised in the shared care protocol or if signs/ symptoms of changes occur consistent with an adverse event
- Report adverse events to the CSM/MHRA via the yellow card system.
- Report adverse events to the consultant sharing the care of the patient
- Stop treatment on advice of specialist, or immediately if intolerable side effects occur provided that it is safer to do so than to continue

Responsibilities of the Patient/Carer

- Discuss potential benefits and side effects of treatment with the specialist and GP. Identify whether they have a clear picture of these from the specialist and to raise any outstanding queries
- Check that where possible the specialists have provided a patient-held record or information sheet for monitoring and/or to alert other clinical staff to the treatment they are receiving
- Share any concerns they have in relation to treatment with the medicine
- Report any adverse effects to their specialist or GP whilst taking the medicine
- Report to the specialist or GP if they do not have a clear understanding of their treatment
- Participate in the monitoring of therapy and the assessment of outcomes, to assist health professionals to provide safe, appropriate treatment

General Guidance:

The following guidance applies to all of the drugs included in this shared care guideline. For specific advice for each drug please refer to the individual drug summaries.

Pregnancy and Breast Feeding
When a patient is prescribed one of these drugs there are significant issues regarding pregnancy and family planning posed by the potency and potential teratogenic potential of these drugs. The decision about when and what drugs should be stopped is a decision that needs to be taken in secondary care. Patients planning a pregnancy should be referred for specialist advice. The decisions potentially affect both male and female patients depending on the drugs being used. The overarching principle is to use the lowest dose to control the disease. Please see the individual drug summaries for specific advice on individual drugs.

Breastfeeding should not be advised if a mother is on one of these drugs, even those felt to be safe during pregnancy, as small amounts are excreted in the breast milk.

Please contact Medicines Information for further advice on use of any of these drugs in pregnancy or breastfeeding.

Exposure to Varicella Zoster Virus
Immunosuppressed Varicella Zoster Virus (VZV) naïve patients have a significant risk of disseminated infection if they contract or are exposed to infection. Therefore, information is passed to all patients in secondary care on immunosuppresant therapy as to what to do if they are exposed or contract chicken pox.

Exposed to VZV and within incubation period

- Previous history of chicken pox
  Only treat if develop active infection; usually aciclovir
- No history of chicken pox
  - Urgent assessment of VZV antibodies
  - If antibody status negative: treatment with pooled immunoglobulin
  - If antibody status positive: only treat with aciclovir if develop infection

Active VZV Infection

- Previous history of infection – treat with aciclovir
- No history of chicken pox
  - Urgent assessment of antibodies
  - Detailed clinical assessment and anti-viral treatment dependent on clinical presentation

Immunisations
No live vaccines should be given to any immunosuppressed patient.[2] All patients on azathioprine, methotrexate, mycophenolate or ciclosporin should be offered annual flu vaccination and the one off

pneumococcal vaccine unless contraindicated. Oral polio should not be given to patients on any of these agents, or to household contacts.

Special Note on Combination Therapy

- **Patients prescribed an immunosuppressant and a Biologic**

Where patients are prescribed both an immunosuppressant and a Biologic the prescribing and monitoring of the biologic will be undertaken in secondary care. GPs participating in shared care will still undertake the prescribing and monitoring required for the immunosuppressant.

The subcutaneous biologics **do not** need any extra monitoring. Virtually all biologics are given with Methotrexate and the usual 3 monthly blood testing is all that is necessary.

Where other monitoring is needed for Biologics, then this will be undertaken in Secondary Care. (For example, pre-infusion immunoglobulin levels).

As with immunosuppressants, Clinicians in Primary Care need to be aware of the increased infection risk in patients prescribed Biologics.

Azathioprine:

Indication
Azathioprine is licensed for the treatment of systemic lupus erythematosus (SLE), dermatomyositis and pemphigus vulgaris.

Azathioprine is also used in a variety of other inflammatory conditions (although unlicensed) including atopic dermatitis, psoriasis, bullous pemphigoid, chronic actinic dermatitis, pyoderma gangrenosum, pityriasis rubra pilaris, Wegener's granulomatosis and cutaneous vasculitis.

Pharmacology
Azathioprine is fully absorbed from the upper GI tract. Peak plasma levels are achieved within 1 to 2 hrs. It is rapidly distributed as little of drug is protein bound. It does not cross the blood-brain barrier. Its action follows in vivo conversion to 6-mercaptopurine and within cells it is converted to purine thioanologues. The key enzyme in the inactivation of thiopurines is thiopurine methyltransferase (TMPT) which is inherited as an autosomal co-dominant trait. Up to 12% of the population have little or no activity in this enzyme, and such individuals can be unusually sensitive to regular doses of azathioprine.

Dose
Azathioprine is given orally in tablet form. The dose used in the management of severe refractory eczema in patients with high or moderate TPMT activity is 1-3mg/kg/day; in patients with intermediate TPMT activity (also known as carrier state) the recommended dose is 0.5-1.5mg/kg/day. It should be taken with or after food, and may be taken in divided doses if preferred.

Monitoring
Baseline tests (To be undertaken by the Dermatology team)
FBC, U&Es, LFTs, 24 hour Urine creatinine if renal function in doubt
Consider TPMT (thiopurine methyl transferase), Hepatitis B and C, and pregnancy testing.

The Dermatologist will assess and monitor the patient's response to treatment until the patient is stabilised, ideally a minimum period of 3 months after initiation.

Routine tests
FBC U+Es and LFTs to be undertaken every 2 weeks for 2 months, then monthly for 4 months and then 3 monthly once the dose and the blood tests are stable. Consider more frequent testing if higher dosage or if renal or hepatic impairment.

Ask about rash, oral ulceration, sore throat, infections or evidence of bruising or bleeding each time. Also ask patients to report these symptoms immediately if they occur while on azathioprine. If patients present with these symptoms perform an urgent blood test. If any of the following occur, stop azathioprine and contact the hospital specialist:

WCC	$< 3.7 \times 10^9$/L
Neutrophils	$< 1.7 \times 10^9$/L
Platelets	$< 150 \times 10^9$/L
AST or ALT	> 3 times the upper limit of the normal range

If any increase in dose revert back to initial monitoring advice.

Adverse Drug Reactions
Mucocutaneous: Urticaria, erythematous rashes, pruritus, oral ulceration.
Haematological: Neutropenia, thrombocytopenia, macrocytosis.
Gastro-intestinal: Nausea (very common), vomiting, abdominal pain and diarrhoea.
Hepatic: Raised transaminases. In the presence of raised transaminases therapy should not be started or continued unless treatment is for autoimmune liver disease.
Renal: Reduce the dose of azathioprine in renal impairment.

Other: Headaches and dizziness.
Conception: Effects of azathioprine on children fathered by men on azathioprine are not known.
Pregnancy: Women planning to become pregnant should not take azathioprine. Benefits considered to be outweighed by the risks.

Breast feeding: Inadvisable for mothers on azathioprine

Opportunistic infections may occur. Infections can require early and vigorous treatment. Treatment may need to be stopped until the infection is clear.

Contraindications
Known hypersensitivity to azathioprine. Hypersensitivity to 6-mercaptopurine should alert the prescriber to probable azathioprine hypersensitivity.

Cautions
Azathioprine should only be used during pregnancy following a careful assessment of risk versus benefit.

Renal impairment: Toxicity may be enhanced. Use doses at the lower end and monitor haematological response.

Hepatic Impairment: Metabolism may be impaired. Regular monitoring required.

Breast feeding: Azathioprine is excreted in breast milk

Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor to minimize the risk of skin cancer and photosensitivity.

Drug Interactions
Allopurinol: Increased toxicity of azathioprine. The dose should be reduced by 75%.

ACE inhibitors: Increased risk of anaemia or leucopenia when azathioprine given with captopril or enalapril.

Antibacterials: Increased risk of haematological toxicity when azathioprine given with co-trimoxazole or trimethoprim.

Anticoagulants: Azathioprine possibly reduces anticoagulant effect of warfarin.

5-Aminosalicylates: Combination of azathioprine with 5-ASAs may possible increase risk of myelosuppression

Clozapine: Increased risk of agranulocytosis when used in combination

Methotrexate:

Indication

Methotrexate is used in the treatment of adults with severe, resistant, unstable or complicated psoriasis.

Pharmacology

Methotrexate inhibits the enzyme dihydrofolate reductase. Its main effect is the inhibition of DNA synthesis, but it also acts directly on both RNA and protein synthesis. It is a folic acid antagonist and is classified as an antimetabolite cytotoxic agent.

The MHRA has noted that Methotrexate is a **weekly** dose and attention should be paid to the **strength** of Methotrexate tablets prescribed and the **frequency** of dosing.

The National Patient Safety Agency has published actions to reduce the risks associated with oral Methotrexate.[10] The issues described in the NPSA alert that relate to shared care guidelines have been incorporated into this guideline.

Dose

Methotrexate is usually taken in tablet form **once a week on the same day of each week.** It should be swallowed whole, not crushed or chewed and taken with food. The usual dose for severe psoriasis that is unresponsive or intolerant to conventional therapy is:

- Initially 7.5mg to 15mg once weekly
- Dose increased by 2.5mg-5mg at 4 weekly intervals according to clinical response
- The maximum oral dose is 25mg once a week

The recommendation is that only 2.5mg tablets should be prescribed and dispensed for patients receiving oral Methotrexate.

Monitoring

Baseline tests (To be undertaken by the Dermatology team)
FBC (incl. differential WCC and platelets), U&E, LFT, urinalysis; chest x-ray and PFT, where there is clinical concern consider baseline chest HRCT; consider pregnancy test.

NPSA MTX monitoring books and patient information should be supplied to all patients

The Dermatologist will assess and monitor the patient's response to treatment until the patient is stabilised

Routine tests
FBC, U&Es, LFTs to be monitored every two weeks until dose stabilised, then monthly for 4 months, then 3 monthly thereafter unless the dose changes. More frequent monitoring may be required if psoriatic arthritis, diabetes, obesity, uncertain alcohol intake or concomitant medication which may reduce the renal excretion of methotrexate.

If patients present with symptoms of potential adverse effects (see below) stop methotrexate and perform an urgent blood test: • If any of the following occur at any time stop medication and contact the hospital specialist:

- WCC $< 3.7 \times 10^9$/L
- Neutrophils $< 1.7 \times 10^9$/L
- Platelets $< 150 \times 10^9$/L
- AST or ALT > 3 times the upper limit of the normal range

Adverse Drug Reactions

Common: Nausea, anorexia, oral ulcers, minor hair thinning, abdominal pain, diarrhoea and headaches, drowsiness, blurred vision
Uncommon: Rash, thrombocytopenia, and neutropenia.
Rare: Hepatotoxicity, Pulmonary toxicity (acute pneumonitis or chronic pulmonary fibrosis).

Any serious reaction to an established drug should be reported to the MHRA via the yellow card system.

The patient should be advised to report any of the following signs or symptoms without delay: Cough, fever, breathlessness, sore throat, bruising, mouth ulcers, jaundice, infections, rash, shingles or chickenpox.

- New or increasing dyspnoea/cough – Withold and discuss with specialist team urgently
- Rash or oral ulceration, nausea, vomiting or diarrhoea – Withold until discussed with member of specialist team
- Abnormal bruising or severe sore throat – Immediate FBC and withhold until result available.

Folic acid 5mg tablets should be taken between one and six days a week, according to the patient and their experience of side effects. Folic acid should NOT be taken on the same day of Methotrexate.

Contraindications

- Profound impairment of renal or hepatic function.
- Haematological impairment.
- Liver disease including fibrosis, cirrhosis, recent or active hepatitis; active infectious disease; and overt or laboratory evidence of immunodeficiency syndrome(s).
- Serious cases of anaemia, leucopenia, or thrombocytopenia.
- Pregnancy or breast-feeding.
- Patients with a known allergic hypersensitivity to Methotrexate

Cautions

Methotrexate should be used with extreme caution in:

- Elderly patients (a lower dose should be considered)
- Patients with ulcerative disorders of the GI tract
- Patients with psychiatric disorders
- Patients exposed to chickenpox. If patients are exposed to chicken pox and are not immunised by prior infection or vaccination they may need passive immunisation with varicella-zoster immunoglobulin if the contact risk is appreciable. Discuss immediately with secondary care.

Drug Interactions

Aspirin / NSAIDs: increased Methotrexate toxicity, sometimes life threatening cases have been reported with concurrent administration, the risk is lowest for those on low dose Methotrexate, with normal renal function. If an NSAID is introduced FBC should be checked one week later.

Co-trimoxazole and trimethoprim must be avoided. Other antibiotics may interact. If a patient who is taking methotrexate, require antibiotics for a bacterial infection, Rheumatology must be consulted for advice about withdrawing Methotrexate temporarily.

Antimalarials

Clozapine

Ciclosporin

Corticosteroids: increased risk of haematological toxicity

Antiepileptics

Leflunomide

Omeprazole: possible increased risk of Methotrexate toxicity

Mycophenolate:

Indication

Mycophenolate is an immunosuppressant drug which has been shown to be of benefit in patients with a variety of skin conditions who are intolerant or unresponsive to standard treatments.

Mycophenolate is used for the following indications (**all unlicensed**):

- systemic lupus erythematosus (SLE)
- lupus nephritis
- inflammatory myopathy such as dermatomyositis and polymyositis
- psoriasis
- atopic dermatitis
- autoimmune bullous dermatoses such as pemphigus.

Pharmacology

Mycophenolate is a reversible inhibitor of inosine monophosphate dehydrogenase and thus inhibits purine synthesis, with potent cytostatic effects on both T- and B-lymphocytes. It is given with other immunosuppressants, for the prevention of graft rejection, and is also used in diseases with an auto-immune or immune-mediated inflammatory component.

Dose

Mycophenolate is given orally as tablets or suspension (NB suspension is branded and more costly than prescribing tablets). The dose used in the management of dermatological conditions is 1 - 2g daily, in divided doses.

Monitoring

Baseline tests (To be undertaken by the Dermatology team)
FBC, U&Es, LFTs, 24 hour Urine and creatinine if renal function in doubt

The Dermatologist will assess and monitor the patient's response to treatment until the patient is stabilised.

Routine tests
FBC and LFTs to be undertaken every week for the first 2 months. The frequency of testing can then be reduced to every 3 months once the dose and the blood tests are stable, or once monthly for the first year for patients with low baseline TPMT levels

Following this first year of treatment, the monitoring frequency can drop to three monthly intervals and the specialist may then ask the GP to take over prescribing and monitoring.

Ask about rash, oral ulceration, sore throat, infections or evidence of bruising or bleeding each time. Also ask patients to report these symptoms immediately if they occur while on immunosuppressants. If patients present with these symptoms perform an urgent blood test. If any of the following occur, stop mycophenolate and contact the hospital specialist:

- WCC $< 3.7 \times 10^9$/L
- Neutrophils $< 1.7 \times 10^9$/L
- Platelets $< 150 \times 10^9$/L
- AST or ALT > 2 times the upper limit of the normal range

Adverse Drug Reactions
Psychiatric and CNS: agitation, confusional state, depression, anxiety, insomnia, convulsions, tremor, somnolence, paraesthesia.
Cardiac: tachycardia, hypotension, hypertension, vasodilation.

Haematological: Leucopenia, thrombocytopenia, anaemia, pancytopenia, leucocytosis, pure red cell aplasia, hypogammaglobulinaemia.
Gastro-intestinal: vomiting, diarrhoea, nausea, GI haemorrhage, peritonitis, ileus, colitis, GI ulceration, gastritis, constipation, dyspespia, flatulence, sepsis, gastrointestinal candidiasis.
Respiratory: pneumonia, respiratory tract infections, pleural effusion, cough, dyspnoea, bronchiectasis.
Skin: skin cancer, benign neoplasm of skin, skin hypertrophy, acne, rash, alopecia.
Hepatic: derangement of LFT's.
Renal: urinary tract infections, renal impairment.
Other: electrolyte disrubances, anorexia, dizziness, headache, pyrexia, chills, oedema, malaise, asthenia, pain.

Pregnancy: It is advised that women taking mycophenolate should not become pregnant as there is insufficient data on teratogenicity. The benefits of continuing treatment in pregnancy should be weighed by the risks on an individual patient basis.

Breast feeding: breastfeeding is contraindicated in women taking mycophenolate, since the drug is excreted into breast milk.

Opportunistic infections may occur. Infections can require early and vigorous treatment. Treatment may need to be stopped until the infection is clear.

Contraindications
Patients with a hypersensitivity to mycophenolate mofetil or mycophenolic acid and in women who are breastfeeding.

Cautions
Mycophenolate should only be used during pregnancy following a careful assessment of risk versus benefit.

Renal impairment: In renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 ml•min^{-1}•1.73 m^{-2}), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Hepatic Impairment: No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Mycophenolate should be used with extreme caution in patients with active serious GI disease and should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor to minimize the risk of skin cancer and photosensitivity.

Drug Interactions
Aciclovir: Mycophenolate has been shown to increase plasma concentrations of Aciclovir when administered concurrently, however, this interaction is unlikely to be clinically significant unless the patient has moderate to severe renal impairment.

Antacids and proton pump inhibitors (PPIs): Decreased mycophenolic acid (MPA) exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered concurrently with mycophenolate. When comparing rates of transplant rejection or rates of graft loss between mycophenolate patients PPIs vs. mycophenolate patients not taking PPIs, no significant differences were seen. These data support

extrapolation of this finding to all antacids because the reduction in exposure when mycophenolate was co- administered with magnesium and aluminium hydroxides is considerably less than when mycophenolate was co-administered with PPIs.

Cholestyramine: following single dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g TID of cholestyramine for 4 days, there was a 40 % reduction in the AUC of mycophenolate. Caution should be used during concomitant administration because of the potential to reduce efficacy of mycophenolate.

Medicinal products that interfere with enterohepatic circulation: caution should be used with medicinal products that interfere with enterohepatic circulation because of their potential to reduce the efficacy of mycophenolate.

Ciclosporin A: ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil.
In contrast, if concomitant ciclosporin treatment is stopped, an increase in mycophenolate AUC of around 30% should be expected.

Ganciclovir: based on the results of a single dose administration study of recommended doses of oral mycophenolate and IV ganciclovir and the known effects of renal impairment on the pharmacokinetics of both mycophenolate and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of mycophenolate pharmacokinetics is anticipated and dose adjustment is not required. In patients with renal impairment in which mycophenolate and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.

Oral contraceptives: the pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected by coadministration of mycophenolate.

Rifampicin: in patients not also taking ciclosporin, concomitant administration of mycophenolate and rifampicin resulted in a decrease in mycophenolate exposure (AUC0-12h) of 18% to 70%. It is recommended to monitor drug exposure levels and to adjust mycophenolate doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sevelamer: decrease in mycophenolate Cmax and AUC0-12 by 30% and 25%, respectively, were observed when mycophenolate was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer mycophenolate at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption. There is no data on mycophenolate with phosphate binders other than sevelamer.

Trimethoprim/sulfamethoxazole: no effect on the bioavailability of mycophenolate was observed.

Norfloxacin and metronidazole: in healthy volunteers, no significant interaction was observed when mycophenolate was concomitantly administered with norfloxacin and metronidazole separately. However, norfloxacin and metronidazole combined reduced the mycophenolate exposure by approximately 30 % following a single dose of mycophenolate.

Ciprofloxacin and co-amoxiclav: Reductions in pre-dose (trough) mycophenolate concentrations of about 50% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or co-amoxiclav. This effect tended to diminish with continued antibiotic use and to cease within a few days of their discontinuation. The change in predose level may not accurately represent changes in overall mycophenolate exposure. Therefore, a change in the dose of mycophenolate should not normally be necessary in the absence of clinical evidence of adverse effects. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Tacrolimus: in hepatic transplant patients initiated on mycophenolate and tacrolimus, the AUC and Cmax of MPA, the active metabolite of mycophenolate, were not significantly affected by coadministration with tacrolimus. In contrast, there was an increase of approximately 20 % in tacrolimus AUC when multiple doses of mycophenolate (1.5 g BID) were administered to patients taking tacrolimus. However, in renal transplant patients, tacrolimus concentration did not appear to be altered by mycophenolate.

Other interactions: co-administration of probenecid with mycophenolate mofetil in monkeys raises plasma AUC of mycophenolate by 3-fold. Thus, other substances known to undergo renal tubular secretion may compete with mycophenolate, and thereby raise plasma concentrations of either mycophenolate or the other substance undergoing tubular secretion.

Ciclosporin:

Indication
Ciclosporin is licensed for severe atopic dermatitis and severe psoriasis when conventional second-line therapy is inappropriate or ineffective.

Pharmacology
Ciclosporin effect and toxicity is dose dependent. It is metabolised by cytochrome p450 isoenzyme CYP 3A4. Drugs may alter ciclosporin levels by inducing or inhibiting this enzyme. Ciclosporin is also transported back into the gut lumen by the intestinal P-glycoprotein which is also inhibitable or inducible by other drugs.

Dose
Ciclosporin comes as an oral capsule in 25, 50 and 100mg doses. Usual starting dose is 2.5 mg/kg daily in divided dose. Usually a 25mg dose increase in dose is introduced every 2 weeks until effective therapy is reached, maximum dose is 5mg/kg or when toxicity occurs. Other regimens may be used by dermatology specialists. Different brands have different bioavailability. It is important that ciclosporin is prescribed by brand so patients are dispensed the same brand each time they collect a prescription.

Monitoring
Baseline tests (To be undertaken by the Dermatology specialists)
FBC, U&Es, LFTs, BP, 24hr Urine Creatinine clearance and GFR are suggested, urate, lipids
Consider pregnancy test

The Dermatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised.

Routine tests
FBC, LFTs, U&Es, Urinalysis, & BP to be monitored every 2 weeks until stable dosage reached. Then monthly for 4 months then every 3 months.
Urate & lipids to be monitored every 2-3 months (Optional)
Blood pressure to be monitored at each blood test
Pay particular attention to serum creatinine and potassium levels

More frequent checks are necessary when the ciclosporin dose is increased, or concomitant treatment with a non-steroidal anti-inflammatory drug is initiated or its dosage increased. Because the pharmacodynamic interaction between ciclosporin and NSAIDs may adversely affect renal function, caution should be exercised if NSAID therapy is to be continued.

If patients present with symptoms of potentially severe adverse effects **stop Ciclosporin** and perform an urgent blood test:

If any of the following occur at any time contact the hospital specialist:
WCC $< 3.7 \times 10^9$/L
Neutrophils $< 1.7 \times 10^9$/L
Platelets $< 150 \times 10^9$/L
AST or ALT > 3 times normal range
Hypertension (BP >160/95 or risen by > 20mmHg from baseline)
Serum creatinine >30% of baseline
Potassium > 5.5 mmol/l

If any increase in dose revert back to initial monitoring advice.

Adverse Drug Reactions *(Please refer to SPC for full list)*
Mucocutaneous: Urticaria, erythematous rashes, pruritus, oral ulceration and gum hyperplasia.

Haematological: Leucopenia, anaemia, thrombocytopenia.
Cardiovascular: Hypertension, oedema, hyperlipidaemia.
Gastro-intestinal: Diarrhoea, (if not severe and tolerable may resolve in time), nausea, dyspepsia.
Hepatic: If transaminases rise >3 times normal range stop drug (rare occurrence).
Renal: Renal impairment and nephropathy are significant and common problems.
Other: Headaches, tremor, fatigue.

Contraindications
Contraindicated in abnormal renal function, uncontrolled hypertension, uncontrolled infections and malignancy. Contraindicated in pregnancy. Ciclosporin crosses placenta and use in pregnancy is associated with premature birth and low birth weight. Patients should be advised not to become pregnant for three months following cessation of treatment.

Cautions
Renal impairment: Ciclosporin can impair renal function
Hepatic Impairment: Ciclosporin may impair liver function. Dosage adjustment may be necessary.
Hyperkalaemia: Ciclosporin can cause hyperkalaemia

Concomitant administration of Non steroidal anti-inflammatory drugs increases the risks of renal impairment. Patients should be closely monitored. In view of the potential risk of skin malignancy, patients on ciclosporin should be warned to avoid excess ultraviolet light exposure.

Patients with impaired renal function (except in nephrotic syndrome patients with a permissible degree of renal impairment), uncontrolled hypertension, uncontrolled infections, or any kind of malignancy should not receive ciclosporin.

Drug Interactions
Many drugs interact with Ciclosporin. Please refer to the Summary of Product Characteristics for a full list.

The following drugs increase ciclosporin serum levels:
Antibiotics – Erythromycin, clarythromycin, fluoroquinolones.
Antifungals – Ketoconazole, itraconazole, fluconazole.
Calcium channel blockers- Diltiazem, verapamil, nicardipine, amlodipine
Other- Colchicine, amiodarone, H2 blockers, grapefruit juice.

The following drugs decrease ciclosporin serum levels: *(*These agents may double the rate of ciclosporin elimination)*
Anti-epileptics – Phenytoin*, carbamazapine*, primidone
Antibiotics – Rifampicin*, sulphonamides, trimethoprim.

Nephrotoxic drugs: Care should be taken when prescribing ciclosporin with other drugs that exhibit nephrotoxic synergy e.g. Aminoglycosides, NSAIDs – in particular diclofenac (halve the diclofenac dose), amphotericin B, methotrexate, ciprofloxacin, trimethoprim)

Ciclosporin may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins) and etoposide. Ciclosporin may enhance the potential of HMG-CoA reductase inhibitors (statins) and colchicine to induce muscular toxicity e.g. muscle pain and weakness, myositis and occasionally rhabdomyolysis.

Caution is required for concomitant use of potassium sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) or potassium containing drugs since they may lead to significant increases in serum potassium.

Shared Care Protocol –remains open to review in light of any new evidence
***Amber** = To be initiated and titrated to a stable dose in secondary care with follow up prescribing and monitoring by primary care.*

Communication

Specialist to GP
The specialist will inform the GP when they have initiated any of these drugs. When the patient is near completing the satisfactory initiation period, the specialist will write to the GP to request they take over prescribing and where possible give an indication as to the expected length of treatment. The Specialist will also send a Shared care request form to support the GP in undertaking shared care. (Appendix A)

GP to specialist
If the GP has concerns over the prescribing of azathioprine, methotrexate, mycophenolate or ciclosporin they will contact the specialist as soon as possible.

Contact Details	Telephone No	Fax No	Email
Consultant Dermatologists Dr Nicola Hardcastle Dr Kay Baxter	 01226 432257 01226 432116	 01226 435233 01226 435233	 nicola.hardcastle@nhs.net kay.baxter2@nhs.net
Medicines Information Gillian Turrell, Lead Pharmacist	 01226 432857	 01226 434431	 gilliansmith2@nhs.net
Dermatology Nurse Specialist Lisa Shaw	 01226 432117	 01226 435233	 l.shaw1@nhs.net

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2. Summary of Product Characteristics. Maxtrex. October 2015. Available at www.medicines.org.uk/EMC/medicine/6003/SPC/Maxtrex+Tablets+2.5+mg/
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5. British National Formulary accessed online at www.medicinescomplete.com October 2015
6. Martindale: The Complete Drug Reference accessed online at www.medicinescomplete.com October 2015
7. Meggit S J, et al. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. *Br J Dermatol 2011: 165: pp711-734*
8. Chakravarty K, et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists (2008). *Rheumatology 31/3/2008.*

Appendix A –Shared Care (Amber) request form

- Specialist to complete when requesting GP to enter a shared care arrangement.
- GP to return signed copy of form.
- Both parties should retain a signed copy of the form in the patient's record.

From (**Specialist**): _____ **To** (**GP**): _____

Patient details

Name: _____ ID Number: _____

Address: _____ DOB: _____

Diagnosed condition: (circle as appropriate)

Systemic lupus erythematosus (SLE) *Lupus nephritis*
Dermatomyositis *Polymyositis*
Atopic dermatitis *Pemphigus/Pemphigoid*
Psoriasis *Other (please state)*_____

Amber Drug details

Drug name: Dose:

Date of initiation: _____ Length of treatment: _____

The patient will be reviewed by the Consultant on: _____

The patient should be reviewed by the GP by: _____

Monitoring

The following monitoring should be undertaken by the GP:

Parameter		**Reference Range**	**Most recent result**	**Date taken**	**Required frequency of monitoring**
FBC	Platelets	150 – 400 x 10^9/L			Every 3 months, next due……..
	Hb	132 – 169g/L (male) 119 – 149g/L (female)			
	WCC	3.7 – 10 x 10^9/L			
	Neutrophils	1.7 – 6.6 x 10^9/L			
LFT	Bilirubin	<21 micromol/L			
	ALT	0 – 40 units/L			
	AST	0 – 40 units/L			
	GGT	0 – 50 units/L			
	ALP	30 – 130 units/L			
U&Es	Creatinine	66 – 118micromol/L (male) 51 – 96micromol/L (female)			
Other					

Communication

Consultant
Telephone number: _____ Fax number:_____

Email address: _____

Specialist Nurse
Telephone number: _____ Fax number: _____

Email address: _____

Confirmation of acceptance of shared care

Specialist (Doctor/Nurse) name: _____

Specialist (Doctor/Nurse) signature: _____ Date: _____

I, Dr ……., can confirm I :

☐ accept the request to participate in shared care for the patient named above.

☐ reject the request to participate in shared care for the patient named above. The reason for this being ……..

GP signature: _____ Date: _____