

Azathioprine, 6-Mercaptopurine, Methotrexate and Mycophenolate for Inflammatory Bowel Disease and Autoimmune Hepatitis

Update November 2019

This guideline has been subject to consultation with Barnsley Consultant Gastroenterologists Dr A Soliman, Dr K Kapur and Dr E Said. The guidance was initially drafted in July 2012 by Gillian Smith (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. The last update has been guided by Fernando Garcia Fuertes (Lead pharmacist).

This guideline has been subject to consultation and endorsement by:

- The Area Prescribing Committee on 8th January 2020

Background Information

Thiopurines (azathioprine and 6-mercaptopurine (6-MP)), and methotrexate are well established drugs in treating Inflammatory Bowel Disease (IBD). Thiopurines are first line and mycophenolate is second line in treating autoimmune hepatitis. Usually patients under treatment for autoimmune hepatitis will be also on prednisolone low dose as directed by gastroenterologist. 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 azathioprine, 6-MP, methotrexate and mycophenolate **are not licensed** for the management of inflammatory bowel disease or autoimmune hepatitis. Their use, however, has strong peer group support amongst Gastroenterologists and Hepatologists, and as such is routinely recommended in national treatment guidelines.

Azathioprine, 6-MP, methotrexate and mycophenolate 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/carers 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 or 4 months for azathioprine and 6-MP, up to 6 months for methotrexate and 4 months for mycophenolate)
- Check for any drug interactions when initiating treatment
- Notify the patient's GP that treatment has commenced (See Appendix A and B for a summary of clinical 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 Gastroenterology 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 gastroenterologist
- 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
- 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.

Exposure to Varicella Zoster Virus

Immunosuppressed Varicella Zoster Virus (VZV) naïve patients have a significant risk of disseminated infection if exposed to or contract infection. Therefore, information is passed to all patients in secondary care on Azathioprine/6-mercaptopurine/steroid therapy as 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 vaccine should be given to any immunosuppressed patient.² All patients on thiopurines, methotrexate or mycophenolate 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.

Thiopurines: (Azathioprine and 6-Mercaptopurine)

Indication

Azathioprine is a pro-drug of 6-MP, and both agents, in addition to methotrexate, are well-established and effective treatment for several conditions including inflammatory bowel disease.

Azathioprine:

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 thioanalogues. 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 inflammatory bowel disease is 2-2.5mg/kg daily, and the dose for autoimmune hepatitis is 1-2mg/kg daily. It should be taken with or after food, and may be taken in divided doses if preferred.

If the patient is initiated on thiopurines as co-adjuvant therapy with biologic therapy due to immunogenicity cover, the target will be stated specifically on the appendix B.

6-Mercaptopurine:

Pharmacology

6-Mercaptopurine is variably and incompletely absorbed from the gastrointestinal tract; about 50% of an oral dose has been reported to be absorbed, but the absolute bioavailability is somewhat lower, probably due to gastrointestinal or first-pass metabolism, and is also subject to wide interindividual variation. Once absorbed it is widely distributed throughout body water and tissues. 6-MP crosses the blood-brain barrier to some extent and is found in the CSF, but only in subtherapeutic concentrations.

The pharmacological action of 6-MP follows intracellular conversion to nucleotide derivatives. The key enzyme in the inactivation of thiopurines is thiopurine methyltransferase 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 susceptible to 6-MP toxicity.

Dose

6-MP is given orally in tablet form. The dose used is 1–1.5 mg/kg daily. It should be taken with or after food, and may be taken in divided doses if preferred.

If the patient is initiated on thiopurines as co-adjuvant therapy with biologic therapy due to immunogenicity cover, the target will be stated specifically on the appendix B.

Since azathioprine is a pre-cursor to 6-MP, the following information is the same for both drugs:

Monitoring

Baseline tests (To be undertaken by the Gastroenterology team)

FBC, U&Es, LFTs, 24 hour Urine creatinine if renal function in doubt

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.

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

Routine tests

FBC, LFTs and U&E's to be undertaken fortnightly for the first 2 months. The frequency of testing can then be reduced to monthly for the next two months, once the dose and the blood tests are stable, patients can repeat FBC, LFTs and U&E's every three months.

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 or 6-MP. If patients present with these symptoms perform an urgent blood test. If any of the following occur, stop azathioprine/6-MP 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/6-MP 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/6-MP. Benefits considered to be outweighed by the risks.

Breast feeding: Inadvisable for mothers on azathioprine/6-MP

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 or 6-MP 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 and 6-MP. 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 or 6-MP given with co-trimoxazole or trimethoprim.

Anticoagulants: Azathioprine and 6-MP possibly reduce anticoagulant effect

5-Aminosalicylates: Combination of azathioprine or 6-MP with 5-ASAs may possible increase risk of myelosuppression

Clzapine: Increased risk of agranulocytosis when used in combination

Thiopurine with Allopurinol - (off licence indication)

Allopurinol is an inhibitor of the Xanthine oxidase/ dehydrogenase (XDH) by affecting the metabolism of thiopurines. Azathioprine and mercaptopurine are metabolised by a series of enzymes in to the favourable metabolite TGN and unfavourable metabolite MeMP (Figure 1). Patients with high levels of TPMT are high methylators with potentially high level of MeMP which is potentially responsible for hepatotoxicity of the drug, whereas high levels of TGN are responsible for dose related toxicity, such as myelosuppression. Allopurinol by inhibiting XDH activity shifts the ratio of TGN/ MeMP in favour of TGN but requires a dose reduction **to** about 25% of usual target dose. Gastroenterologist must approve concomitant use as discussed with the IBD pharmacist.

The use of allopurinol with thiopurines is indicated when patients presents hepatotoxicity induced by thiopurines (monotherapy) or when patients are intolerant with full clinical target.

According to clinical practice we normally initiate patients on a dose of 50mg of allopurinol alongside with thiopurines at 25% target dose. The dose will be increased to 100mg of allopurinol when thioguanine nucleotide report shows a ratio TGN:MeMP still above 11.

Methotrexate:

Indication

Methotrexate is used in the treatment of adults with severe, active Crohn's disease who fail therapy or response to maintain remission with thiopurines.

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 inflammatory bowel disease or autoimmune hepatitis that is unresponsive or intolerant to conventional therapy is:

- Initial dose is 25mg weekly subcutaneous injections for 16 weeks then switch to oral tablets.
- After completion of 16 weeks period, the dose can be reduced to maintenance dose 15mg oral tablets weekly.
- The maximum oral dose is 25mg once a week

If the patient is initiated on methotrexate as co-adjuvant therapy with biologic therapy due to immunogenicity cover, the target will be stated specifically on the appendix B.

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 Gastroenterology team)

- FBC (including differential WCC and platelets), U&E, LFT, urinalysis and chest x-ray (If any abnormality), Pro-collagen peptide 3.

The Gastroenterologist 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 for two months, then monthly for four months and then three monthly thereafter.

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 – Withhold and discuss with specialist team urgently
- Rash or oral ulceration, nausea, vomiting or diarrhoea – Withhold 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 autoimmune hepatitis who are intolerant or unresponsive to azathioprine, or other standard treatments.

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 autoimmune 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 autoimmune hepatitis is 2g daily, in divided doses, often in combination with prednisolone low dose for at least 2 years under gastroenterologist supervision.

Monitoring

Baseline tests (To be undertaken by the Gastroenterology team)

FBC, U&Es, LFTs, 24 hour Urine creatinine if renal function in doubt

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

Routine tests

U&E, FBC and LFTs to be undertaken fortnightly for the first two months, then monthly for two further months, then three monthly thereafter.

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 x 10⁹/L
- Neutrophils < 1.7 x 10⁹/L
- Platelets < 150 x 10⁹/L
- AST or ALT > 3 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, dyspepsia, 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 disturbances, 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 $< 25 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$), 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.

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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 (AUC_{0-12h}) 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 C_{max} 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

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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.

Live vaccines: live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished.

Communication

Specialist to GP The specialist will inform the GP when they have initiated azathioprine, 6-mercaptopurine (6-MP), methotrexate or mycophenolate. 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 and B)			
GP to specialist If the GP has concerns over the prescribing of azathioprine, 6-MP or methotrexate, they will contact the specialist as soon as possible.			
Contact Details	Telephone No	Fax No	Email
Consultant Gastroenterologist Dr A Soliman Dr K Kapur Dr D Bullas Dr E Said Dr R Atkinson Dr V Sathyanarayana	01226 432715 01226 432715 01226 432715 01226 432715		a.soliman@nhs.net kapil.kapur@nhs.net elmuhtady.said@nhs.net
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Pharmacy-led IBD/AIH Clinic Gillian Turrell Fernando Garcia Fuertes Neermala Sanassee Pharmacist IBD Clinic	01226 432857 01226 432817 01226 432309 01226 432777	01226 434431 01226 434431	gilliansmith2@nhs.net fernandogarciafuertes@nhs.net n.sanassee@nhs.net pharmacist.ibdclinic@nhs.net
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References

1. Summary of Product Characteristics. Imuran. December 2014. Available at: www.medicines.org.uk/EMC/medicine/2882/SPC/Imuran+Tablets+50mg/
2. Summary of Product Characteristics. Maxtrex. December 2014. Available at www.medicines.org.uk/EMC/medicine/6003/SPC/Maxtrex+Tablets+2.5+mg/

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.

3. Summary of Product Characteristics. Cellcept. January 2015. Available at <http://www.medicines.org.uk/emc/medicine/1679>
4. British National Formulary. Number 67 September 2014. Available at www.medicinescomplete.com
5. Martindale: The Complete Drug Reference accessed online at www.medicinescomplete.com December 2014
6. Gleeson D, Heneghan M A. British Society of Gastroenterology (BSG) guidelines for the management of autoimmune hepatitis. *Gut* 2011

Appendix A

Dear <GP name>,

<Patient> <Hospital Number> has been monitored on <Drug> for <disease>, which has been well tolerated, as per shared care guidelines the patient will be reviewed by <Gastroenterologist>. All relevant clinical information for future monitoring has been documented on appendix B.

Appendix B - Shared Care request form

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

Patient details

Name	(automatic generated from Winvoice)
NHS number	(automatic generated from Winvoice)
Date of Birth	(automatic generated from Winvoice)

Amber Drug details

Drug name	
Dose	
Frequency	
Date of initiation	
Length of treatment	
Co-adjuvant therapy (if applicable)	

	Date	Date	Date	Date
Thiopurinemethyltransferase (TPMT) (thiopurines only)				
Thioguanine level (TGN) (thiopurines only)				
Methylmercaptopurine (MeMP) (thiopurines only)				
Ratio TGN:MeMP (thiopurines only)				
Pro-collagen peptide (P3NP) (methotrexate only)				

Next Blood Monitoring

The patient is stable on the medication above. The blood tests for U&E, FBC and LFT should be undertaken by the GP every three months after signing this shared care agreement.	
Next blood test is due	Date:

Confirmation of acceptance of shared care (Please fax document once signed within 14 days)

	Name	Signature	Date
Gastroenterologist			
GP			
Gastroenterology secretaries for any enquiry - Fax number: 01226432792			
Lucy Adam (lucyaldam@nhs.net); Nicola Walker (nicolawalker@nhs.net); Helen Tune (helentune@nhs.net)			
IBD Nurses	Debbie West (deborah.west3@nhs.net); Rachel Gray (rachel.gray4@nhs.net)		
Pharmacist IBD clinic	pharmacist.ibdclinic@nhs.net		

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To save resources you have been sent appendix A and B of the shared care document. The full document (Azathioprine, 6-Mercaptopurine, Methotrexate and Mycophenolate for Inflammatory Bowel Disease and Autoimmune Hepatitis, *date approved January 2020*) can be accessed on the Barnsley BEST website at the following link:

<http://best.barnsleyccg.nhs.uk/clinical-support/medicines/shared-care-guidelines/>

Or via the Barnsley Area Formulary www.barnsleyformulary.nhs.uk