DMARDs in Adult Rheumatology Shared Care Information
Azathioprine

Please also refer to the Shared Care Guidelines - Principles of Shared Care and Responsibilities of Speciality Team, GP, Pharmacist & Patient

Indications:
- *Licensed* - RA, SLE, dermatomyositis & polymyositis
- *Unlicensed* - Vasculitides such as polyarteritis & giant cell arteritis, psoriasis, psoriatic arthritis

Time to response:
- 6 -12 weeks

Presentation and Availability:
- 25mg and 50mg tablets

Contra-indications:
- Thiopurine methyl transferase (TPMT) deficiency (homozygous state)
- Lesch Nyhan Syndrome – due to congenital HGPRT deficiency
- Co-prescription with:
  - Allopurinol: inhibits Azathioprine metabolism
  - Cotrimoxazole and trimethoprim: can cause life- threatening haematotoxicity
  - Aminosalicylates (mesalazine, sulphasalazine, olasalazine): may cause bone marrow toxicity

Thiopurine methyl transferase (TPMT) deficiency:
A TPMT level must be checked prior to commencing Azathioprine as it can predict potential toxicity:

TPMT Level	Risks	Azathioprine Dose Adjustment
Above normal Range	No risk	Higher doses may be required
Heterozygous Deficiency	Possible serious toxicity which may not be evident for first 6 months	Prescribe with caution Reduce dose May require more frequent blood tests
Homozygous Deficiency	Serious and fatal toxicity can occur within 6 weeks	Do not prescribe

Side effects:
- *Rarely:* Hypersensitivity reaction including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis – immediate withdrawal of drug advised
- *Serious effects:* Liver impairment, cholestatic jaundice, blood dyscrasias (see monitoring)

See SPC for full details: http://www.medicines.org.uk/emc/default.aspx

Pregnancy and fertility & breastfeeding:
- Women should not conceive while on Azathioprine. It should not be prescribed in pregnancy
- Where benefit of continuing treatment outweighs potential risks to an unborn child, the specialist will need to make a careful risk versus benefit assessment, discuss this with patient and the patient should remain under specialist supervision
- Dose reduction at 32 weeks of gestation may prevent neonatal leucopenia
- Evidence of mutagenicity is equivocal in men
- Breastfeeding is contraindicated

Drug Interactions:
- Allopurinol, Co-trimoxazole, Trimethoprim, Aminosalicylates – as above
- Warfarin: inhibition of anticoagulant effect of has been reported
- ACE inhibitors: co-prescription may cause anaemia and leucopenia (if significant consider an alternative to ACE or a different DMARD
- Phenytoin, Sodium Valproate, Carbamazepine: Azathioprine reduces the absorption of these drugs

See SPC for full clarification of interactions: http://www.medicines.org.uk/emc/default.aspx

Vaccination:
- See Appendix i

Azathioprine – Dosage and Monitoring

Dosage and Administration:
- 1mg/kg per day
- Increase after 4-6 weeks up to 3mg/kg per day
- In elderly or hepatic/ renal impairment – use dose at the lower end of the range

Pre-treatment assessment:
- Full blood count (FBC)
- Urea and electrolytes (U&Es) and Creatinine
- Liver function tests (LFTs)
- TPMT assay

During treatment:
See 'Responsibilities of Speciality Team, GP, Patient and Pharmacist in Shared Care Agreement'

Investigation	Frequency	Specialist	GP
FBC and LFTs	Weekly for 6 weeks Continue 2 weekly until dose stable for 6 weeks Check 2 weeks after any dosage change then monthly	✓	
FBC and LFTs	Check monthly If dose is stable for 6 months, consider reducing frequency to 3 monthly In heterozygote TPMT patients, continue monthly monitoring as a minimum		✓
U&Es and Creatinine	6 monthly		✓

- Please check ESR and CRP as indicated by the specialist team (usually every 3-6 months) to help in monitoring disease activity and treatment response

Action to be taken if:

WBC< 3.5 x 10^9/l	Withhold until discussed with speciality team
Neutrophil <2.0 x 10^9/l	Withhold until discussed with speciality team
MCV > 105 fl	Check B12, Folate and TSH – If low, start appropriate supplementation – If normal, discuss with specialist team
Platelets <150 x 10^9/l	Withhold until discussed with speciality team
AST, ALT > 2 fold rise (from upper limit of reference range)	Withhold until discussed with speciality team
Creatinine clearance 10-20 ml/min	Withhold until discussed with speciality team
Rash or oral ulceration	Withhold until discussed with speciality team
Abnormal bruising or sore throat	Withhold until FBC available & discuss with speciality team

- A rapid fall or a consistent downward trend in any value should also prompt caution and extra vigilance

Appendix i

Guidelines for vaccinations in patients taking immunosuppressants, steroids and biological therapies

This is the BSR's most recent guidance and is subject to revision and formal review

GENERAL INFORMATION LIVE VACCINES

- Live vaccines are contraindicated while on immunosuppressive therapy
  - e.g Azathioprine, Ciclosporin, Leflunomide, Mycophenolate, Cyclophophamide
- Immunosuppressive therapy should be stopped for 3 months prior to live vaccine administration
- Live vaccines if needed should be ideally given at least 2 weeks, preferably 4 weeks, before immunosuppressive therapy is commenced
- In immunosuppressed patients, the immunological response may be suboptimal. Consider repeating 3 months after therapy has ceased if viral titres low
- Consider using immunoglobulins if contact risk is significant (e.g. Varicella, Measles)

INACTIVE VIRUS VACCINES

- In immunosuppressed patients, the immunological response may be suboptimal but can be given in accordance with national recommendations
- There is an increased risk in the immunocompromised from secondary bacterial infections following influenza
- Pneumococcal and the Annual flu vaccination is recommended in patients with autoimmune inflammatory rheumatic disease
- Immunisation against Meningococcal, Haemophilus B, Tetanus and Hepatitis B infection might be indicated. Check Hepatitis B titres 3 months after the 3rd injection
- Check Varicella zoster titres prior to immunisation if appropriate

VACCINES FOR TRAVEL ABROAD

- Yellow fever vaccine must not be given. Patients should be advised not to travel to countries requiring this e.g. mid-Africa. If travel necessary, an exemption statement may be accepted but the patient will be at risk
- Polio vaccine - the oral live polio vaccine (OPV) must not be given. Killed inactivated vaccine can be given but may need to be obtained from abroad so adequate notice must be given
- Typhoid vaccine - the live form should not be given. Killed vaccine is available but only 70% protective
- Inactive viruses can be given e.g. Rabies, Anthrax, Cholera, Plague

VACCINES FOR HOME

- Polio - OPV is contraindicated and in household contacts. Inactivated form (IPV) can be used
- Measles, Mumps, Rubella (MMR) - all three live vaccines is contraindicated but not in household contacts. Exposure to measles should be treated with immunoglobulin regardless of prior immunization
- BCG is contra-indicated. Consider giving it in juvenile arthritis 4 weeks before immunosuppressives started. Juvenile arthritis patients should be brought up to date with vaccination schedules prior to receiving methotrexate

Zostavax (Zoster Vaccination)

- A live attenuated vaccine with high antigen level of varicella zoster virus
- Eligible individuals previously not immunised should receive a single dose of vaccine at least 14 days (preferably a month) before starting immunosuppressive therapy as the risk and severity of shingles is considerably higher amongst immunosuppressed individuals
- Zostavax should not be given to a person who is receiving immunosuppressive therapy such as high-dose corticosteroids
- Zostavax can be given to patients receiving low dose corticosteroids, low dose methotrexate (<0.4/kg/week) and azathioprine (<3.0mg/kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis and sarcoidosis

- Immunosuppressed individuals who are inadvertently vaccinated with Zostavax should be urgently assessed by a clinician to establish the degree of immunosuppression and the need for prophylactic acyclovir. If a varicella rash develops following inadvertent vaccination, patients can be treated with aciclovir

See link for full guidance:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/239892/2013181_Shingles_QA_for_healthcare_professionals_final.pdf

PATIENTS ON STEROIDS

- Live vaccines must not be given to patients taking moderate or high doses of steroids for longer than 2 weeks
- Long-term moderate to high dose steroids should be stopped for 3 months before live vaccines can be administered

There are no contra-indications to using live vaccines if steroid therapy is:

- for less than 2 weeks
- by topical application
- by intra-articular or soft tissue injection
- used as replacement therapy in physiological doses e.g. adrenal insufficiency
- long-term low dose steroids (10mg per day or less)

BIOLOGICS

- Live vaccines should not be given concurrently with biological therapies as no data is available on the effects of vaccination in these patients e.g. anti TNF- therapy, Tocilizumab or Anakinra

LEFLUNOMIDE

- The long half-life of Leflunomide should be considered when contemplating administration of a live vaccine after stopping the drug

References

- BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with British Association of Dermatologists. Rheumatology. 2008 K Chakravarty *et al* http://rheumatology.oxfordjournals.org/content/suppl/2008/05/31/kel216a.DC1/kel216b.pdf

- SPC (Summaries of Product Specification) for each drug are available on the EMC website: http://www.medicines.org.uk/emc/default.aspx Please ensure you refer to the correct brand where appropriate (especially for ciclosporin and mycophenolate mofetil) as some information is brand specific.

- Vaccinations in the immunocompromised person guidelines for the patient taking immunosuppressants, steroids and the new biologic therapies January 2002 http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/v/vaccinations_in_the_immunocompromised_person.pdf

- BSR statement on Vaccination in Adult Patients with Rheumatic Diseases November 2011