DMARDs in Adult Rheumatology - Shared Care Information

Ciclosporin

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

Indications
- Licensed - Rheumatoid arthritis (RA), psoriasis and atopic dermatitis

Time to response:
- Up to 12 weeks

Presentation and Availability:
- 10mg, 25mg, 50mg and 100mg capsules
- Oral sugar free solution 100mg/ ml
- Injection 50mg/ ml
- Careful monitoring is required when switching between capsules and oral solution as bioequivalencies vary

Contraindications:
- Uncontrollable hypertension
- Renal or liver failure (in RA patients)
- Severe electrolyte imbalance e.g. hyperkalemia
- Suspected systemic infections or sepsis
- Patients under 18 years (in RA patients)

Cautions:
- Pregnancy and lactation
- Grapefruit juice must be avoided for 1 hour before or after taking ciclosporin as it increases bioavailability
- Malignancy such a lymphomas

Side effects:
- *Common non-life threatening*: Burning sensation in hands and feet (usually during the first weeks of treatment), nausea, tremor, abdominal discomfort may occur initially but usually subsides, gum hyperplasia, poor apetite, increased hair growth
- *Rare:* Hypertension, nephrotoxicity, hepatotoxicity (see monitoring)

See SPC for full list of side effects: http://www.medicines.org.uk/emc/default.aspx

Pregnancy and Breastfeeding:
- Reliable contraception should be prescribed for men and women – consult rheumatologist
- Breastfeeding is contraindicated

Drug Interactions:
- Lipid regulating drugs – simvastatin maximum dose 10mg/day
- NSAIDs - increased nephrotoxicity, **reduce dose of diclofenac by 50%**
- Digoxin – may increase serum levels of Digoxin
- Methotrexate – increased toxicity
- Avoid St Johns Wort – decreases Ciclosporin activity
- Colchicine -avoid
- Avoid Tacrolimus, Lercanidipine
- Potassium sparing diuretics

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

Vaccination:
- See Appendix i

Ciclosporin – Dosage and Monitoring

Dosage and Administration (in Rheumatoid Arthritis):
- Initiate at 2.5mg/kg per day in 2 divided doses for 6 weeks
- Increase in 25mg increments to a maximum of 4mg/kg per day
- Often effective at doses between 2.5-3.2mg/kg/day

Pre-treatment assessment:
- FBC, LFTs, U&Es. Check Creatinine on 2 occasions 2 weeks apart to obtain a mean value
- Creatinine clearance and fasting lipids
- Blood pressure should be below 140/90mmHg on 2 separate occasions 2 weeks apart. If greater, treat before starting Ciclosporin
- In patients with psoriasis, check the patient for all forms of pre-existing tumours, including those of the skin and cervix. Skin lesions, which are not typical of psoriasis, must be biopsied before treatment to exclude skin cancers, mycosis fungoides or other pre-malignant disorders
- In patients with psoriatic arthritis, assess whether the patient has received PUVA. If the total dose of PUVA exceeds 1000 J discuss with dermatologists

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

Investigation	Frequency	Specialist	GP
FBC and LFTs	Monthly until the dose is stable for 3 months	✓	
	3 monthly thereafter		✓
U&E and Creatinine	Every 2 weeks until the dose is stable for 3 months	✓	
	Monthly thereafter		✓
Fasting serum lipids	6 monthly		✓
Blood pressure	At each monitoring clinic visit Maintain below 140/90		✓

- Please monitor CRP/ ESR (usually every 3 – 6 months) to assess disease activity as requested by specialist team

Action to be taken if:

Creatinine >30% rise from baseline	Repeat in 1 week if still > 30% above baseline, withhold until discussed with speciality team
Potassium rise to above normal range	Withhold until discussed with speciality team
Platelets <150 x 10^9/l	Withhold until discussed with speciality team
AST, ALT, Alkaline Phosphatase >X2 upper limit of reference range	Withhold until discussed with speciality team. Check any other reasons e.g. alcohol, drug interaction (including over the counter medication)
Abnormal bruising	Check FBC urgently and withhold until discussed with speciality team
High BP: if >140/90 on 2 consecutive occasions 2 weeks apart	Consider treating hypertension before stopping ciclosporin. Stop if BP cannot be controlled. Also discuss with speciality team
Significant rise in fasting lipids	Withhold until discussed 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