DMARDs in Adult Rheumatology - Shared Care Information

Methotrexate

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

Indication:
- *Licensed* – Rheumatoid arthritis (RA) and Psoriasis
- *Unlicensed* – Psoriatic arthritis (PsA), Connective tissue disease (SLE, myositis and vasculitis) and Felty's syndrome

Presentation and Availability:
- **Oral:** 2.5mg and 10mg tablets but **ONLY the 2.5mg tablet** should be prescribed and dispensed for patients covered by this shared care guideline. See 'Recommendations to GP'
- **Subcutaneous injection:** may be used if the maximum oral dose is not effective or tolerated

Time to response:
- 6 weeks to 3 months

Contraindications:
- Pregnancy and breastfeeding
- Suspected local or systemic infection
- Bone marrow failure with uexplained anaemia and/ or cytopenia
- Immunodeficiency syndromes
- Hypersensitivity to methotrexate or any of the excipients

Cautions:
- Renal impairment
- Alcohol consumption should remain well within the national recommended limits

Side Effects:
- *Common:* Nausea, diarrhoea, stomatitis
- *Less common:* Headaches, drowsiness, blurred vision
- *Serious effects:* Hepatic, pulmonary and bone-marrow toxicity can occur acutely at any time during therapy. A low neutrophil count is of most concern and can present with high fever and sore throat. Serious pulmonary adverse effects with acute breathlessness have been recorded

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

Pregnancy and Breastfeeding:
- Methotrexate is a teratogenic and abortificient drug thus all male and female patients should not conceive for at least 3 months after stopping methotrexate
- Female patients should be prescribed or offered contraception during treatment and until 3 months after drug is stopped
- Breastfeeding is contraindicated

Drug Interactions:
- NSAID's and salicylates – excretion of methotrexate may be impaired leading to toxicity but co-prescription of methotrexate with NSAID's is quite common in rheumatology practice and a clinically significant interaction is rare. NSAIDs should be discontinued if liver function derangement occurs
- Co- trimoxazole and Trimethoprim – anti- folate effect of methotrexate is increased and greatly increases the risk of bone marrow aplasia. **DO NOT CO-PRESCRIBE**
- Clozapine – avoid concomitant use due to increased risk of agranulocytosis
- Ciclosporin - can increase Methotrexate toxicity. The specialty team will provide patient- specific advice on co- prescriptions
- Probenecid - Methotrexate excretion is reduced leading to toxicity

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

Vaccination:
- See Appendix i

Methotrexate – Dosage and Monitoring

Dosage and Administration (in Rheumatoid arthritis):
- Typical initial dose is 5- 10mg **ONCE WEEKLY** orally
- Increased by 2.5mg every 1-6weeks to 15-20mg weekly as needed
- Maximum dose 25mg weekly
- **I**n elderly or significant renal impairment, use lower doses

Folic acid: Co- prescribe 5- 10mg once weekly (on a **DIFFERENT** day to methotrexate, preferably the day after) to minimise the risk of minor side effects and to improve compliance

Subcutaneous methotrexate disposal: The Rheumatology Specialist Nurses will provide a mauve top cytotoxic sharps bin. Bins ready for disposal should be returned to the Rheumatology Department at Hemel Hempstead and St Alban's City Hospital and to The Helen Donald Unit at Watford General Hospital

Pre-treatment Assessment:
- FBC, U&Es and Creatinine, LFTs
- Chest X-ray (unless performed in the last six months)
- Pulmonary function tests (consider in selected patients)
- PIIINP (not as standard in RA and PsA patients as levels can be affected by disease itself)

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

Investigation	Frequency	Specialist	GP
FBC and LFTs	2 weekly until dose and monitoring stable (usually 3 months)	✓	
	Monthly thereafter until dose and disease stable for 1 year		✓
	Thereafter reduced frequency (8-12 weekly) as advised by specialist		✓
U&E and Creatinine	6-12 monthly (more frequently if there is any reason to suspect deteriorating renal function)		✓

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

Action to be taken if:

WBC <3.5 x 10^^{9}/l	Withhold until discussed with specialist team
Neutrophil <2.0 x 10^9/l	Withhold until discussed with specialist team
Platelets <150 x 10^9/l	Withhold until discussed with specialist team
MCV >105fl	Check B12, Folate & TFT and start supplementation if required. Discuss with specialist team if necessary
ALT, AST twice upper limit of reference range	Withold until discussed with specialist team
Albumin – unexplained fall	Withhold until discussed with specialist team
Rash, oral ulceration, nausea or diarrhoea	Withhold until discussed with specialist team
Abnormal bruising or sore throat	Withhold until FBC result available & discuss with speciality team
New or increasing dyspnoea or dry cough	Withhold and discuss urgently with specialist team
Significant deterioration in renal function	Withhold until discussed with specialist team

- In addition to absolute values for haematological indices a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance

Folinic Acid Rescue:
- Used in overdose or severe bone marrow toxicity under specialist direction
- Administer calcium folinate by intravenous infusion in doses up to 75mg within 12 hours
- Then administer 4 doses of 12 mg intramuscularly every 6 hours

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