Methotrexate..

What Should We Tell Patients?

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Methotrexate at West Suffolk Hospital

- MTX starts at 15 mg /wk
  - optimal start dose*.
  - DMARD escalated according to protocol if DAS$_{28}$ > 2.6
  - * K Visser and D van der Heijde ARD 2009;68:1094-109

- Week 5 phone clinic .... MTX 20mg
- Week 10 nurse clinic...MTX 25mg.
- Week 15 doctor clinic...s/c MTX
Methotrexate at Morriston Hospital, Swansea

- MTX starts at 7.5mg or 10mg/wk (depending on level of disease activity)
  - DMARD escalated according to protocol if DAS$_{28}$ >2.6 (ie increasing by 2.5mg every 6 weeks until on maximum licensed dose of 25mg)
  (BSR/BHPR DMARD guidelines 2008)

- Follow-up (F/U) at week 6-8

- Depending on clinical response at this time
  - F/U at week 12-14 and then at 24-28 thereafter.
Methotrexate & Varicella Zoster Virus (VZV) & Herpes Zoster (HZ)

A 32 year old office worker with a aggressive new onset of RA is referred to you to start Methotrexate. You ask her if she has ever had Chicken pox she is unsure.

How would you proceed. Would you:-

- Undertake any screening?
- Offer immunisation.
The Guidelines

- BSR /BHRP (2008) Guideline does not include screening for VZV.

- RCN (2013 - update currently in publication) suggest checking varicella zoster is important.

- BSPAR – recommends VZV screening & vaccination in children.
The Evidence.

• No evidence to support the link between MTX & VZV infection in patients with RA. However, immunosuppressed patients may have more severe symptoms.

• 90% of the adult population in the UK have immunity to VZV.

• If VZV vaccination is given (live vaccine) 2 doses are required 8 weeks apart with a delay of 2-4 weeks prior to commencing MTX.
Guidelines for HZ

- HZ vaccination recommended for the over 60 age group who have no contraindications with inflammatory disorders receiving low dose methotrexate (0.4 mg/kg/week).


- **NB ...this is a live vaccine.**
Conclusion.

• The data regarding the role of MTX & VZV is conflicting.

• The role of pre MTX screening is controversial & should not delay treatment.

• Uncertainty regarding pre MTX VZV screening.
Reference


• Zhang N et al (2012) Does Methotrexate increase the risk of varicella or herpes Zoster infection in patients with RA. A systematic literature review. Clinical Experimental Rheumatology Nov-Dec;30(6);962-71
A 59 year old female patient with RA has been taking oral MTX 10mg/week and Folic acid 5mg 6 days a week (re: nausea – which has not helped).

She has therefore been referred to your clinic to be switched from oral to s/c.

She is also flying to Spain, and has asked for your advice about the travel requirements for the MTX injections.

Please discuss what you would advise with regard:
- The start dose of s/c MTX for this patient?
- The cytotoxic handling of the s/c MTX injections? ie gloves/spillage etc
- Taking s/c MTX injections away with her to Spain?
Switching from oral MTX to subcutaneous MTX.

Rationale for this:
• Increased tolerability &
• Bioavailability


In Swansea - if suboptimal response is noted or patients experience GI side-effects with oral MTX at 15mg/week :

-> oral MTX switched to s/c MTX

• Follow-up regimen for switch patients is the same as initial start for oral MTX:
  • Follow-up (F/U) appointment at week 6-8
  • Depending on clinical response at that time:
    - F/U at week 12-14 and then at 24-28 thereafter
What start dose of s/c MTX would you advise for the patient?

- No specific recommendation re: dosage of MTX when switching from oral -> s/c

- However caution needs to be exercised when switching to s/c MTX, as it has been reported that the bioavailability of MTX can be increased by 30% (Braun et al 2008)

- Blood monitoring of the above?
  - No specific recommendations for this.
  - However, in light of the above evidence – we organise fortnightly monitoring for 6 weeks and then monthly thereafter, if stable.
What advice would you give about the cytotoxic handling of s/c MTX?

- **Cytotoxic risk considered low** when used in the treatment of inflammatory arthritis – ie small doses, small risk *(Wong et al (2009)) and especially now s/c MTX is available in sealed pre-filled, pre-dosed syringes with an attached needle.

- Gloves? – *RCN (2013 - updated - to be published s/c MTX doc)* recommends: gloves not required for patients, but that HCP/carers should wear gloves and observe good hand washing protocols when administering s/c MTX *(Crauste-Manciet et al 2005, Dougherty & Lister 2011)*

- Spillage on skin? - *Wong et al (2009)*, found poor dermal methotrexate penetration from deliberate contamination. If MTX accidentally spilt on skin -> area needs to washed liberally with soap and cold water. Do not scrub as unbroken skin provides protection. *(Weinstein & Plumer 2007, Dougherty & Lister 2011)* Patient to contact GP/Rheumatology team is she has any adverse reactions.

- Spill kit? *RCN (2013 - updated - to be published s/c MTX doc)* suggests whilst spill kits are unlikely to be needed – HCP’s need to adhere to local policy.
What advice would you give the patient about taking her s/c MTX injections abroad with her?

- s/c MTX storage varies according to local health policy and the manufacturer’s recommendations. Patient should be advised to:
  - check the box for instructions and
  - with rheumatology team if unclear.

- Recommended that patients keep their s/c injections in their hand luggage, in case they get mislaid or damaged or freeze in the hold. *(Medac 2012).*

- If required - a covering letter from Rheumatology department can be obtained re: transportation of s/c MTX

- If the patient is not happy to take s/c injections away with her, oral MTX can be taken instead, whilst she is away. *(RCN 2013 – updated - to be published s/c MTX doc)*
Conclusion.

- Plethora of evidence to support that s/c MTX has improved tolerability and bioavailability over oral MTX

- No specific recommendations re: dosage and/or monitoring of MTX when switching to s/c MTX - decision based on local specialist clinical experience and judgement

- The cytotoxic handling of s/c MTX (esp pre-dosed, pre-filled syringes) more evidence to support -> **low risk**
  - Adherence to local policy/manufacturer’s SPC/advice/best practice guidance is key in promoting best practice.

- Storage of s/c MTX is variable & dependent on local health policy and the manufacturer’s recommendations
  - Patients & HCP need to aware and knowledgeable of the s/c MTX supplied.
References:


References:


• RCN (2013) – recently updated and to be published doc – Administering subcutaneous methotrexate for inflammatory arthritis RCN Guidance (second edition)


A 32 year old patient with psoriatic arthritis is well controlled on MTX 20 mg /week & folic acid 5 mg/week. She attend your clinic & asks you...

“I want to get pregnant what should I do about my Methotrexate?”

Please discuss what you would advise

• length of washout period.
• Dose of folic acid.
• Effect on fertility
Methotrexate & Pregnancy

- MTX demonstrates significant teratogenicity. Skull & limb abnormalities are the most frequent.
- The risk of exposure to MTX in the 1st trimester is 10/42 chance of abnormality in the fetus.
- 4/13 case of exposure of low dose MTX have resulted in abnormal fetuses.
How long should women stop MTX before conception

- The presence of MTX in the liver has been reported 116 days after exposure.
- Oncology patients are advised a 12 month washout.
- Manufactures advice re recommended washout period for low dose MTX varies between 3- 6 months.
How Long Should Male Patients Stop MTX

- Theoretical risk of sperm mutation in males treated with MTX.
- However a study looking at men with RA on low dose MTX found no significant chromosomal breakage.
- The duration of individual spermatogenesis is approx 74 days.
- The recommendations for male patient is 3-6 month washout.
Folic acid/ folinic acid

- Recommended that women who wish to become pregnant should be offered folinic acid for at least 5 months
Methotrexte...Fertility & Breast Feeding

• The risk of infertility appears low even after high-dose MTX this is for both men & women

• MTX is excreted into breast milk in low concentrations. It is not known whether these small amounts are potentially harmful the advice therefore is avoidance of MTX during breast feeding
Information & Reporting

OTIS.. Organisation of Teratology Information Specialists