

The use of methotrexate in rheumatological conditions

A review of the evidence

Maureen Cox
January 2009



Visser et al

- Multinational evidence based recommendations for the use of methotrexate in rheumatic disorders with a focus on RA: Integrating systematic literature research and expert opinion of an international panel of rheumatologists in the 3E Initiative. (ARD online 2008 Nov 25th)



Katcahmart W

- The efficacy and toxicity of methotrexate monotherapy vs mtx combination therapy with non biologic DMARD's : A systematic review and meta analysis

(ARD online 2008 December 3rd)



Objective

- To develop evidence based recommendations for the use of methotrexate in daily clinical practice in rheumatic disorders



Method

- 751 rheumatologist for 17 countries participated in 3E initiative of 2007-2008 consisting of 3 separate rounds of discussion and delphi votes
- 10 clinical questions concerning the use of methotrexate were formulated
- Systematic literature review medline, embase, cochrane library, 2005-2007 ACR / Eular absracts (graded)
- Multinational recommendations (10) formulated and agreed
- Assessment of the potential impact on clinical practice



1. Pre mtx work-up

- To include:
 - Clinical assessment of risk factors for mtx toxicity including (alcohol intake)
 - Patient education
 - LFT's, albumin, FBC, creatinine
 - CXR (within previous year)
 - Consider serology for HIV, hepatitis, fasting blood glucose, lipid profile, and pregnancy test

(No of articles reviewed 52. Level of evidence 4. Grade of recommendation C. Agreement mean 8.2)



2. Dose

- Oral dose should be started at 10-15 mg/ wk, with escalation of 5 mg every 2-4 weeks up to 20-30 mg /wk, depending on clinical response and tolerability.
- Consider parenteral administration for inadequate response or intolerance

(No of articles reviewed 50. Level of evidence 2b.
Grade of recommendation B. Agreement mean 7.8)



3. Folic Acid supplementation

- Prescription of at least 5mg Folic Acid per week is strongly recommended
 - Meta analysis 9 studies suggest folic acid reduces liver and GI toxicity without reducing efficacy
- Only folinic acid < 5mg wk significantly decreased GI side effects and hepatotoxicity, but at doses of > 5mg wk significantly increased no of tender and swollen joints.

(No of articles reviewed 9. Level of evidence 1a. Grade of recommendation A. Agreement mean 7.5)



4. Safety monitoring

- When starting Mtx or increasing the dose, ALT +/- AST, creatinine, and FBC should be performed every 1-1.5 months until a stable dose is reached, and every 3 months thereafter.
- Clinical assessment for side effects and risk factors should be performed at each visit.

(No of articles reviewed 23. Level of evidence 4.
Grade of recommendation C. Agreement mean
8.1)



5. Hepatotoxicity

- Mtx should be stopped if there is a confirmed increase in ALT/ AST >3 times ULN but may be reinstated at a lower dose following normalisation.
- If ALT/AST are persistently elevated up to 3 time ULN the dose should be adjusted.
- Diagnostic procedures should be considered in case of persistent elevated ALT /AST > 3 times ULN after discontinuation

(No of articles reviewed 46. Level of evidence 2b. Grade of recommendation C. Agreement mean 7.4)



6. Long term safety

- Based on its acceptable safety profile, mtx is appropriate for long term use.
 - RA pts on mtx compared to pts without mtx, had a lower mortality incidence rate (23 /1000 vs 26.7 /1000 pt years) and reduced cardiovascular mortality in a large 6 yr prospective study.
 - Long term use not associated with increased risk of serious infections
 - 5 case reports suggested that mtx might be associated with EBV related lymphoproliferative disease and regression after mtx withdrawal

(No of articles reviewed 88. Level of evidence 2b. Grade of recommendation B. Agreement mean 8.7)



7. Monotherapy vs combination therapy

- In DMARD naïve pts the balance of efficacy and toxicity favours mtx monotherapy over combination with other conventional DMARD's
- Mtx should not be considered as the anchor for combination therapy when mtx monotherapy does not achieve disease control
- Recommendation does not contradict well established superiority of combination with prednisone or anti TNF therapies

(No of articles reviewed 20. Level of evidence 1a. Grade of recommendation A. Agreement mean 8.3)



8. Methotrexate as a steroid sparing agent

- MTX as a steroid sparing agent, is recommended in GCA and PMR and can be considered in pts with SLE or juvenile dermatomyositis.
- No studies were found comparing the steroid sparing affect of other DMARD's

(No of articles reviewed 6. Level of evidence 1b. Grade of recommendation B. Agreement mean7.7)



9. Management of the peri-operative period

- Mtx can be safely continued in the peri - operative period in RA patients undergoing elective orthopaedic surgery
- No studies were found regarding elective non orthopaedic surgery

(No of articles reviewed 4. Level of evidence 1b. Grade of recommendation B. Agreement mean 8.8)



10. Before / during pregnancy

- Mtx should not be used for at least 3 months prior to a planned pregnancy for males and females, and should not be used during pregnancy or breast feeding.

(No of articles reviewed 6. Level of evidence 4. Grade of recommendation C. Agreement mean 8.2)



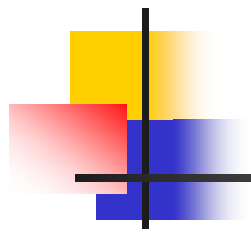
Changes in practice

	Will change practice (%)	Already current practice (%)	I don't want to change (%)
1. Pre mtz workup	29.8	61.2	9.0
2. Dose	16.1	68.7	15.1
3. Folic Acid	15.3	78.6	6.1
4. Monitoring	21.1	53.5	25.4
5. Hepatotoxicity	16.5	68.0	15.5



Changes in practice (2)

	Will change practice (%)	Already current practice (%)	I don't want to change (%)
6. Long term safety	2.0	96.0	2.0
7. Mono vs combination	5.0	86.9	8.1
8. Steroid sparing agent	25.6	67.1	7.3
9. Peri-operative	41.3	46.7	12.0
10. Pregnancy	19.5	71.3	9.2



Thank you.

Questions?