Scottish Paediatric and Adolescent Rheumatology Network (SPARN)

Guideline for Methotrexate blood monitoring

NOTE

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Screening and recommendations before starting:

Prior to commencing ensure:

- core data set for patient disease recorded in clinical notes
- baseline bloods including FBC, ESR and CRP, liver transaminase levels, serum creatinine, VZ IGG (+Measles IGG if unclear Measles history or vaccine status) taken
- documented
    - decision to start methotrexate with the dose, route, frequency **(WEEKLY)**, supply pathway.
    - if Paediatric rheumatology nurse specialist has delivered appropriate education regarding the medication
    - provision of information leaflets
- agree training / administration plan
- blood monitoring schedule agreed and in place
- consider:
    - Varicella immunity. If negative, vaccination should be recommended, safe to give on Methotrexate below 15mg/m2 (see SPARN VACCINE guidelines)
    - Measles immunity / vaccination status. If negative, consider vaccination, safe to be given on Methotrexate below 15mg/m2 (see SPARN vaccine guidelines)
    - see SPARN vaccine guideline regarding other DMARDs and vaccination

Blood monitoring and follow up schedule:

Interpreting blood-monitoring results is challenging and evidence guiding intervention lacking. Raised liver transaminases encountered during monitoring may be the result of factors other than methotrexate. Ortiz-Alvarez (2004) showed 95% of blood abnormalities were due to intercurrent infections, in teen population covert alcohol consumption should be considered.

Withholding doses of methotrexate is likely to decrease disease control. Therefore, intervention must consider the likeliest cause of the blood test result abnormality and balance risks.

Cut off values for individual patients may be personalised, acknowledging known variations (e.g. lower cut-off values for white cell counts in people of certain ethnic origins, SLE patients as WCC may be low and will only restore with good disease control).

These ranges differ from BSR and BNF recommendations (MARAJIA 2018), during COVID reduced testing did not increase rate of results detected out with normal ranges (Costello et al 2022 & Wood et al 2023).

Frequency of testing:

Check bloods by week six of starting methotrexate treatment (or after changing the dose of methotrexate). Minimum set is Full Blood Count (FBC) and liver function tests (ALT/AST). Frequently ESR (or PV), CRP are taken in addition as disease assessment measures.
If bloods within normal ranges, check FBC and LFT again by week 12.
At week 24, take, FBC, LFT, CRP & UE. Other tests may be required based on diagnosis
After this testing can be at 3 monthly intervals.
If patient on other medications that affect liver function or bone marrow, eg isotretinoin, monitoring bloods should default to most frequent recommendation at minimum 4 weekly for first 6 months for Methotrexate.
Nakafero et al (2023) showed significant risk factors for MTX toxicity were (in descending order),

- previous raised LFTs
- stage 3 kidney disease
- anti-epileptic medications
- IDDM
- MCTD
- long term paracetamol use

For patients with these risk factors, more frequent monitoring should be considered at medication commencement.

If bloods out with normal ranges:

- any fall in FBC counts repeat in 7 days
- LFT above normal range but below 3x ULN, bloods to be repeated in 2 to 4 weeks, can remain on MTX

When to consider suspending methotrexate and retest if:

- platelet count less than 150x109/L
- white cell count less than 3x109/L
- Neutrophils less than 1.5x109/L
- Lymphocytes less than 0.5x109/L
- Haemoglobin less than 90mg/dL (without another identifiable cause)
- AST or ALT above three times the upper limit of the normal range
    - LFTs above 3x ULN (but below 500), suspend Methotrexate, investigate for common other possible causes of raised LFTs and repeat bloods in 2 to 4 weeks and reassess
    - where LFT are above 500 investigations of liver function should be undertaken, see acute liver investigations guidelines at www.bspghan.org.uk/hepatology-guidelines plus discussion

investigation of other possible causes (check frequency of administration, contaminant drug use, alcohol, infections etc), consider urgent referral to Hepatology for review/ management

When to consider restarting methotrexate:

Can be restarted once bloods have returned to normal. All patients who have had medication paused due to blood levels out with expected norms should have more frequent bloods at restart, spaced no more than 4 weekly for 3 months.

When to omit methotrexate dose:

- If on an acute course of antibiotics, avoid trimethoprim / Ciprofloxacin
- If they have pyrexia of known origin (caution patients with MAS/SoJIA may have pyrexia due to their condition and MTX should be given in this situation)

When to stop methotrexate:

- if LFT do not return to normal, do not restart without discussion with Hepatologists
- if nausea or lethargy, effecting life unless no alternative therapy options available
- signs of bone marrow suppression

Other information:

Practical tips for administration of subcutaneous methotrexate can be found in the RCN document “Administering subcutaneous methotrexate for inflammatory arthritis” available on the RCN website www.rcn.org.uk.
Play therapy / psychology may be helpful if patients struggle with injections / bloods tests.

Drug interactions:

Please see current British National Formulary for Children (BNFC) for an up-to-date list of interactions. Of note, the sulphonamides antibiotics (including co-trimoxazole) can induce bone marrow suppression in combination with MTX and should be avoided.

Additional considerations surgery:

Methotrexate therapy need not routinely be stopped in the perioperative period, although individualised decisions should be made for high-risk procedures.

Fertility / pregnancy / breastfeeding:

Known Embryotoxicity and teratogenicity therefore methotrexate should be avoided in young women either contemplating pregnancy, or those who are sexually active and not using reliable methods of contraception. Risk returns to normal 6 months after stopping MTX.

Vaccination:

Please see:

- SPARN vaccine Protocol re general advice about live and inactivated vaccines on UK standard Schedule
- annual SPARN Flu statement. We recommend annual influenza immunization. Live Attenuated Influenza Vaccine (LAIV) recommended if MTX on only
- Covid19 vaccination recommended
- check Pneumococcal vaccine status (part of standard UK schedule)

Folic acid supplementation:

This is standard practice in adults, to reduce haematologic changes and to reduce nausea. There is little supporting evidence in Paediatrics. Due to diet (Folic is fortified into bread and cereals) most children under 10 are unlikely to require supplementation. In children older than 10 supplementation need increases. If given it is usually given once weekly at 5mg not on Methotrexate day, alternatively 1mg or in some centres 5mg daily apart from MTX day is used.

Nausea:

Symptoms may improve with subcutaneous rather than oral medication.

- withholding NSAID on day of methotrexate
- eating a soft sweet during injection can help
- giving on Friday or Saturday night may reduce school absence
- psychological support may be beneficial
- use of antiemetics is common, typically Ondansetron

Safety:

Methotrexate is only given as a **ONCE WEEKLY** dose, regardless of route. It is good practice to administer the same day each week for safety purposes and to promote concordance. The national patient safety association recommend families are advised of the dose and frequency and given written information.

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