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DMARD MONITORING GUIDELINES – Reviewed 23.01.15

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The current BSR DMARD and Denosumab Monitoring Guidelines are now available via the following link: http://www.rnhrd.nhs.uk/our-services/for-clinicians

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a pro-drug of the active metabolite of mycophenolic acid. It is a suppressor of T and B cell proliferation and adhesion and inhibits inosine monophosphate dehydrogenase that eventually blocks the progression to DNA synthesis and proliferation [1]. It does not inhibit the production of interleukins as does ciclosporin and tacrolimus.
MMF has routinely been used in organ transplantation for many years and this remains the licensed indication for its use.

A. Indications: (Unlicensed) RA [2], systemic lupus erythematosus and lupus nephritis [3] and inflammatory myopathy such as dermatomyositis and polymyositis [4, 5]. It has also been used in psoriasis [6], atopic dermatitis and autoimmune bullous dermatoses such as pemphigus. It is also being used in randomized clinical trials in scleroderma, vasculitis and Behcet's disease (Prof. Chris Denton, Royal Free Hospital, London, personal communication).

B. Mycophenolate mofetil dosage: Grade of evidence: C
Typical dose: 1–2 g/day.
Starting dose: 500mg daily for the 1st week, 500 mg twice daily for the 2nd week and increase it gradually by 500 mg each week until the optimal or maximum tolerated dose is reached.
Maximum dose: Up to 3 g/day [2].

C. Route of administration:
Oral tablets (250mg capsules) and suspension.
i.v. infusion–available (see BNF).

D. Time to response: 6 weeks to 3 months

E. Cautions: Grade of evidence: C

(1) Patients with suspected lymphoproliferative disorder or unexplained anaemia, leucopenia and thrombocytopenia.
(2) Localized or systemic infection.
(3) Very frail and elderly.

F. Contraindications: Grade of evidence: C

(1) Pregnancy and breast feeding.
(2) Localized or systemic infections.

G. Notable drug interactions (refer to BNF and SPC)
(1) Antacids: Containing aluminium and magnesium hydroxide cause a decrease in the absorption of MMF by 33% and bioavailability by 17% [7].
(2) Cholestyramine: May decrease the absorption of MMF and bio-availability by 40% [8].
(3) Probenecid: Prevents renal tubular secretion and causes an increase in plasma concentration of MMF.
(4) Aciclovir: Causes increase in the concentration of both MMF and aciclovir. However, the increase is significant only in renal impairment.

H. Common untoward effects

MMF does not usually cause major organ toxicity [9]. The drug does not cause any mutagenic or chromosome abnormalities [10, 11]. The commonest adverse reactions are as follows:

(1) **Gastrointestinal:** Diarrhoea, nausea, vomiting, abdominal cramps and dyspepsia.
(2) **Uro-genital:** Sterile haematuria, urinary tract infection, renal tubular necrosis.
(3) **Haematological:** Abnormal bruising with or without sore throat may indicate bone marrow failure. Severe neutropenia occurs in 0.5% patients receiving MMF in the full dose. STOP the drug. Check FBC immediately and also discuss with specialist team.
(4) **Malignancy:** Lymphomas caused by oncogenic viruses and skin tumours.

I. Monitoring schedule: Grade of evidence: C

	BSR	**BAD**
(a) Pre-treatment assessment	**FBC, U&E, LFTs, CXR.**	**Same as BSR.**
(b) Monitoring	**FBC weekly until dose stable for 4 weeks, then fortnightly for 2 months. Monthly, even after patient is stabilized on treatment.**	**Same as BSR.**

J. Actions to be taken: Grade of evidence: C

WBC <3.5 x 10^9/l	**Withhold until discussed with the specialist team.**
Neutrophils <2.0 x 10^9/l	**Withhold until discussed with the specialist team.**
Platelets <150 x 10^9/l	**Withhold until discussed with the specialist team.**
Bruising with or without sore throat	**Check FBC immediately and discuss with specialist team.**

K. Immunisation

(a) Patients receiving MMF must not receive immunization with live vaccines. Inactivated polio is available although suboptimal response may be seen.
(b) Annual flu vaccination is recommended.
(c) In patients receiving MMFexposed to chickenpox or shingles, passive immunization should be carried out using VZIG.

L. Caveats:

(1) Infections: It is very important to be observant about any new symptoms of infection as the reported incidence of cytomegalovirus infection is slightly higher [6]. The incidence of infection and sepsis is somewhat similar to that typically observed in the transplant population and it is believed that concentrations of mycophenolic acid do not affect the phagocytosis and killing of the bacteria by the neutrophils [12]. In clinical studies, the incidence of herpes, aspergillus and candida were the same whether mycophenolate or azathioprine was used. Pneumocystis carinii pneumonia was almost non-existent in patients treated with MMF [13].

(2) Leucopenia and neutropenia: It is often difficult to assess the exact cause of leucopenia or neutropenia because many causes may lead to the development of these disorders such as additional immunosuppressive regimens, concomitant medications and viral infections or combination of all the above. It is most commonly seen within the first 6 months. Temporary suspension of MMF for 10–14 days will usually result in recovery of the cell count. Once the cell count recovers, the drug can be re-administered in half the

previous dose and gradually increased until a stable dose is attained without any toxic effect [14].

(3) Malignancies: An increased incidence of non-Hodgkin's lymphoma has been documented in transplant patients receiving MMF. The majority of malignancies are B cell lymphoma associated with Epstein-Barr virus [15]. However, concomitant treatment with drugs such as azathioprine, ciclosporin or tacrolimus can increase the probability of lymphoma [15].

(4) Pregnancy and breast feeding: It is generally advised to ensure that the patients are NOT pregnant before the drug is commenced and advised to use contraception for at least 6 weeks after discontinuation of treatment [8]. It is not recommended for mothers who are breast feeding (manufacturer's advice).

References

Mycophenolate mofetil

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