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DMARD MONITORING GUIDELINES – reviewed 23.01.15

RNHRD GP TELEPHONE ADVICE LINE (from 11.00am to 1.00 pm daily): 07747 630875

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

Azathioprine

A. Indications:

(Licensed)
RA, dermatomyositis and polymyositis, autoimmune and chronic active hepatitis, pemphigus vulgaris.

(Unlicensed)
Vasculitides, such as polyarteritis and giant cell arteritis [1] and systemic lupus erythematosus, psoriasis and psoriatic arthritis, severe eczema, bullous dermatoses
including pemphigoid, inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease.

B. Dose: Grade of evidence: B

Typical dose: 1 mg/kg/day—increasing after 4–6 weeks to 2–3 mg/kg/day.

C. Route of administration:

Oral or intravenous—The latter is very irritant and should be used only if oral route is not
feasible. (The intravenous route is hardly ever used in rheumatology.)

D. Time to response:

6 weeks to 3 months

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E. Cautions: Grade of evidence: C

(1) Thiopurine methyl transferase (TPMT) deficiency (heterozygous state): May be associated with delayed haematotoxicity including bone marrow toxicity. Please see section subsequently on TPMT [2].
(2) Sunscreens and protective covering should be encouraged to reduce sunlight exposure [3].
(3) Localized or systemic infection including hepatitis B or C and history of tuberculosis.

F. Contraindications: Grade of evidence: C

(1) Immunization with live vaccines (see section J1).
(2) Pregnancy and breast feeding except in clinically indicated cases (see section on pregnancy) (see section J2).
(3) TPMT deficiency (homozygous state): Avoid, can be fatal (see section J3) [2].
(4) Individuals with Lesch-Nyhan Syndrome due to congenital hypoxanthine-guanine phosphoribosyl transferase (HGPRT) deficiency.

G. Notable drug interactions (refer to BNF and SPC)

(1) Allopurinol: Azathioprine dose should be reduced to 25% of the original dose [4].
(2) Warfarin: Azathioprine inhibits the anticoagulant effects of warfarin [4–6]. Alternatively, consider increasing the dose of warfarin.
(3) Phenytoin, sodium valproate, carbamazepine: Azathioprine reduces the absorption of these drugs.
(4) Angiotensin-converting enzyme (ACE) inhibitors: Co-prescription of azathioprine may cause anaemia [3, 4] (if significant, consider alternative to ACE inhibitor or different DMARD).
(5) Aminosalicylates i.e. mesalazine, olsalazine, balsalazide or sulfasalazine, may contribute to bone marrow toxicity.
(6) Co-trimoxazole and trimethoprim can cause life threatening haematoxicity [3, 4].

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H. Monitoring schedule: Grade of evidence C

	BSR	BAD
(a) Pre-treatment assessment	FBC, U&E, creatinine, LFTs and TPMT assay.	Same as BSR
(b) Monitoring	FBC and LFTs weekly for 6 weeks and continue every 2 weeks until dose stable for 6 weeks; then monthly.	FBC, LFTs weekly until stable on maintenance dose.
	If maintenance dose is achieved and stable for 6 months, consider discussing with patient to reduce monitoring to 3-monthly.	Same as BSR
	In people heterozygote for TPMT, monitoring should continue at monthly intervals at minimum (see section J3).	Same as BSR
(c) Following changes in dose	Repeat FBC and LFTs 2 weeks after dose change and then monthly.	Same as BSR
(d) Regular review	U&E and creatinine should be repeated 6-monthly.	Same as BSR

I. Actions to be taken: Grade of evidence B.

WBC < 3.5 x 10^9/l	Withhold until discussed with specialist team.
Neutrophils < 2.0 x 10^9/l	Withhold until discussed with specialist team.
Platelets < 150 x 10^9/l	Withhold until discussed with specialist team.
AST, ALT > twice upper limit of normal	Withhold until discussed with specialist team.
Rash or oral ulceration	Withhold until discussed with specialist team.
MCV > 105 fl	Check serum folate and B12, and TSH. Treat any underlying abnormality. If results normal, discuss with specialist team.
Abnormal bruising or severe sore throat	Withhold until FBC results available, and discuss with specialist team.

MCV: mean corpuscular volume, TSH: thyroid-stimulating hormone.

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J. Caveats:

(1) Immunization [7]:

(a) Patients receiving azathioprine should not receive immunization with live vaccines. However, the RNHRD have produced specific local guidance with regards to the varicella-zoster vaccine which can be found at http://www.rnhrd.nhs.uk/our-services/for-clinicians, under the heading "Zostavax GP guidelines".

(b) Inactivated polio is available although suboptimal response may be seen.
(c) Annual flu vaccination is recommended.
(d) In patients receiving azathioprine exposed to chickenpox or shingles, passive immunization should be carried out using varicella zoster immunoglobulin (VZIG).

(2) Pregnancy and breast feeding:

(a) Women of childbearing potential should be advised to use effective contraceptive precautions. Evidence of mutagenicity is equivocal in men. In most cases, azathioprine
should not be prescribed if there is a possibility of pregnancy, although there may be some circumstances where the benefit of continuing treatment outweighs the possible risks related to the unborn child. A careful assessment of risk vs benefit is advised. Dose reduction at 32 weeks of gestation may prevent neonatal leucopenia.
(b) Women treated with azathioprine should not breast feed [3, 4, 8, 9].

(3) TPMT assay: This assay provides additional information of risks related to treatment but does not replace routine monitoring [10, 11]. However, for those with higher levels of
serum TPMT, higher doses of azathioprine may be required.

Homozygous deficiency is associated with serious and fatal toxicity that may occur within 6 weeks of starting azathioprine [11].

Heterozygous deficiency is also linked to serious adverse events, although the symptoms may not be evident until 6 months after commencing treatment. Minor unrecognized infections or drug interactions, particularly when co-prescribed with aminosalicylates, such as sulfasalazine, mesalazine or olsalazine, may precipitate fatal
toxicity. Heterozygous individuals should be prescribed azathioprine with caution and, in particular, reduced drug dosage.

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References

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