South West Strategic Clinical Network
Somerset, Wiltshire, Avon and Gloucestershire (SWAG) Cancer Services

Information leaflet for non-haematological physicians: Monoclonal gammopathy of undetermined significance (MGUS)

DEFINITION: MGUS is defined by a monoclonal immunoglobulin (M-protein or paraprotein) in the serum of up to 30g/L in the absence of lytic bone lesions, anaemia, hypercalcaemia and renal insufficiency that is related to the underlying monoclonal plasma cell proliferation and less than 10% plasma cells in the bone marrow. It is a potential precursor to myeloma or related disorders and needs long term follow up once detected.

PREVALANCE/ASSOCIATIONS: The prevalence of MGUS is 3% per persons > 70 years, but is higher in African/Caribbeans than Caucasians. The commonest type of M-protein is IgG, followed by IgM, then IgA. IgM paraproteins are associated with lymphoproliferative disorders(LPD) such as Waldenstrom's Macroglobulinaemia (WM), B cell non-Hodgkin's lymphoma (B-NHL) or chronic lymphocytic leukaemia (CLL), rather than myeloma.

CLINICAL WORKUP/INVESTIGATIONS: Once detected a series of staging investigations are done, which include: FBC, U&E, LFT, calcium, Igs, serum free light chains (SFLC) and spot urine for Bence Jones protein (BJP). The patient should then fall into one of the two categories below:

Blood results / symptoms	Action
ALL of the following: Asymptomatic Normal full blood count, renal function, calcium, immunoglobulins M-proteins**:** IgG<15g/L, IgA/M <10g/l Negative BJP Normal SFLC ratio	Myeloma or related disorder is unlikely to be present. No further investigation necessary, however will need monitoring - see below for guidance

Note: IgM paraprotein – Examine patient to rule out lymphadenopathy/hepatosplenomegaly as evidence of an underlying LPD. If detected consider CT scan.

Blood results / symptoms	Action
ANY of the following: Symptomatic Unexplained abnormal blood results e.g. anaemia, renal impairment M-proteins: IgG>15-g/l, IgA/M>10g/l, IgD/E of any level Positive BJP Abnormal SFLC ratio	Refer to haematology

RISK OF PROGRESSION: The risk of progression to myeloma or related disorder is 1% per year. The most important predictors of progression are the level and isotype of the M-protein. The level in grams/litre is roughly equivalent to the risk of progression for that patient at 10 years following detection. Non-IgG MGUS patients are most at risk of progression.

Level of paraprotein	Risk of progression over 10 years
5g/L	5%
20g/L	20%

MONITORING: Monitoring in primary care is suitable for patients with an M-protein present at the following levels (see table) in whom there are no symptoms, signs or results of initial investigations suggestive of myeloma, other lymphoproliferative disorder or AL amyloidosis.

Paraprotein isotype	Paraprotein quantification
IgG	< 15g/L
IgA	< 10g/L
IgM	< 10g/L

In the first year after identification of MGUS 3–4 monthly testing is advisable reducing to 6–12 monthly as long as there are no symptoms suggestive of progression.

Monitoring blood tests are as follows:

- quantification of the M-protein and immunoglobulin levels
- full blood count
- creatinine; urea and electrolytes, corrected calcium

When monitoring an individual M-protein level clinicians should be aware that inter-laboratory variation can be as high as 25%. Where possible, M-protein quantification repeated over time should be performed by the same methodology in the same laboratory.

Monitoring of symptoms:

Patients and clinicians need to be aware of relevant clinical symptoms. Examples of these and actions that might be taken before requesting review from the haematology service are: back pain – evidence of myeloma bone disease on X-ray; renal impairment - not explained by other medical conditions; anaemia - not explained by haematinic deficiency.

Criteria for re-referral/further investigation:

Patients should be referred to the haematology service under the following circumstances:

- If the concentration of the M-protein increases by more than 25%, (a minimum absolute increase of 5 g/l)
- If symptoms compatible with a diagnosis of myeloma or lymphoma develop
- If unexplained anaemia, other cytopenias or abnormal renal function or hypercalcaemia develop

Even if a patient is seen by the physician at 3-monthly or even more frequent intervals symptoms may rapidly develop in the meantime. The patient is the best person to be aware of the onset of relevant symptoms. It is **essential**, therefore, that patients are fully aware of important symptoms and they should be encouraged to report these outside appointment visits if they occur. Provision of a **patient information leaflet** is advisable (see attached Macmillan information leaflet).

Reference: UK Myeloma Forum and Nordic Myeloma Study Group: guidelines for the investigation of newly detected M-proteins and the management of MGUS. B J Haem, 147, 22–42.