Hevylite: New strategies for Diagnosis, Monitoring and Prognosis of monoclonal gammopathies

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and Binding Site Ltd
How good are tests for monoclonal proteins?

1. Diagnosis – sensitive and specific
   - FLC: +
   - Igs: +

2. Monitoring – reproducible
   - FLC: +
   - Igs: +/-

3. Prognostic
   - FLC: +
   - Igs: -
Diagnosis
Problems with IgG, IgA and IgM assays

1. There is no Igκ/Igλ ratio
2. Nephelometry measures the total immunoglobulin but the patient is Ig’κ or Ig’λ
SPE Analysis of MRC MM VII Presentation Samples
Problems with IgG, IgA and IgM assays

1. There is no Igκ/Igλ ratio
2. Nephelometry measures the total immunoglobulin but the patient is Ig’κ or Ig’λ
3. Scanning densitometry is not accurate
4. IgA bands may be hidden with transferrin
Immunoglobulin molecule and Hevylite (HLC) epitopes
Different heavy chain/light chain immunoglobulins

- IgGκ
- IgGλ
- IgAκ
- IgAλ
- IgMκ
- IgMλ
IgA Multiple Myeloma

![Graph showing IgA lambda vs IgA kappa concentrations in g/L.](image)
Monitoring
Problems with IgG, IgA and IgM assays

1. There is no Igκ/Igλ ratio
2. Nephelometry measures the total immunoglobulin but the patient is Ig’κ or Ig’λ
3. Scanning densitometry is not accurate
4. IgA bands may be hidden with transferrin
5. Haematocrit and plasma volume changes affect immunoglobulin measurements
Effect of volume changes on Ig' measurements

IgGκ- 50g/L
Ig’κ/Ig’λ
= 3/1

IgGκ- 30g/L
Ig’κ/Ig’λ
= 3/1

IgGκ- 20g/L
Ig’κ/Ig’λ
= 3/1
Relationship of monoclonal immunoglobulin changes to plasma volume and haematocrit

Problems with IgG, IgA and IgM assays

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4. IgA bands may be hidden with transferrin
5. Haematocrit and plasma volume changes affect immunoglobulin measurements
6. IgG metabolism is variable
IgG metabolism is controlled by cellular recycling receptors
FcRn binds IgG and albumin

Albumin

IgG

FcRn

“Neonatal or Brambell receptor”
Recycling of IgG

Non-specific uptake

Endothelial cell

IgG binds to FcRn receptor

Degradation

Bound IgG is recycled
IgG FcRn receptors are saturated at normal IgG concentrations.
Relationship between immunoglobulin concentrations and serum half-life
Hence, % changes in IgG measurements depend upon the initial concentrations

For example:-
A patient with 100g/L of IgG and 100% tumour kill by chemotherapy has an 80% fall of IgG in 15 days (100 to 20g/L)

A patient with 10g/L of IgG and 100% tumour kill by chemotherapy has only a 20% fall of IgG in 15 days (10 to 8g/L)

Thus, comparison of reductions in IgG concentrations in patients is not reliable

What does a partial response really mean?
What does a partial response really mean?

Prognosis
Problems with IgG, IgA and IgM assays

1. There is no Igκ/Igλ ratio
2. Nephelometry measures the total immunoglobulin but the patient is Ig’κ or Ig’λ
3. Scanning densitometry is not accurate
4. IgA bands may be hidden with transferrin
5. Haematocrit and plasma volume changes affect Immunoglobulin measurements
6. IgG metabolism is variable
7. Monoclonal IgG, IgA and IgM measurements have no prognostic value and are not in any guidelines
Monoclonal immunoglobulin concentrations

Hevylite ratios - 0.01>HLCr>200

Un-involved immunoglobulins
Comparison of prognostic factors in MM

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del_13</td>
<td>0.03* (n=283)</td>
<td>0.546</td>
</tr>
<tr>
<td>T4_14</td>
<td>0.05* (n=252)</td>
<td>0.515</td>
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<tr>
<td>Del_17p</td>
<td>0.08 (n=277)</td>
<td>0.457</td>
</tr>
<tr>
<td>β₂M&gt;5.5mg/L</td>
<td>0.51 (n=308)</td>
<td>0.407</td>
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<tr>
<td>β₂M&gt;3.5mg/L</td>
<td>0.001* (n=308)</td>
<td>0.045*</td>
</tr>
<tr>
<td>Albumin&lt;35g/L</td>
<td>0.153 (n=302)</td>
<td>0.828</td>
</tr>
<tr>
<td>FLC Tertiles</td>
<td>0.589 (n=307)</td>
<td>0.689</td>
</tr>
<tr>
<td>Monoclonal Tertiles**</td>
<td>0.16 (n=300)</td>
<td>0.748</td>
</tr>
<tr>
<td>200&lt;HLC&lt;0.01</td>
<td>0.017* (n=308)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

* p<0.05 is considered significant
**SPE densitometry measurement
Conclusions for Hevylite

1. **Diagnosis**: More sensitive than SPE and IFE in patients at presentation and with residual disease

2. **Monitoring**: Provides more accurate quantitation than SPE and IFE, particularly at low concentrations

3. **Prognosis**: Better than current markers
Acknowledgements

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J Overton and others at The Binding Site
What makes a good cancer test?

1. Diagnosis – sensitive and specific
2. Monitoring – quantitative and reproducible
3. Prognostic
sFLCs at myeloma presentation are prognostic
ISS for progression in 338 IFM patients

$\beta_2m + \text{albumin}$

$\beta_2m + \text{hevylite ratio}$

$p = 0.023$

$p = 0.000013$