Update in MGUS, SMM and AL amyloidosis

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## Disclosures

<table>
<thead>
<tr>
<th>Research Support/P.I.</th>
<th>Janssen Research and Development, Prothena</th>
</tr>
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<tbody>
<tr>
<td>Employee</td>
<td>None</td>
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<tr>
<td>Consultant</td>
<td>Janssen Research and Development</td>
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<tr>
<td>Major Stockholder</td>
<td>None</td>
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<td>Speakers Bureau</td>
<td>None</td>
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<tr>
<td>Honoraria</td>
<td>GSK</td>
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<tr>
<td>Membership in Advisory Board</td>
<td>Janssen Research and Development</td>
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<tr>
<td>Presentation includes a description of the following off-label use of a drug or medical device</td>
<td>Doxycycline</td>
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Spectrum of plasma cell disorders

MGUS
Low risk  Int/high risk

SMM
Low risk  High risk

Multiple myeloma
Biomarker of malignancy  Myeloma defining event

Tumor progression
Monoclonal gammopathy
IgG/IgA/light chain

M-protein disease

Genetic, epigenetic and microenvironmental abnormalities
End-organ damage

MGRS and others
AL amyloidosis

Survival
MGUS
Surveillance of MGUS

- Current guidelines suggest life-long, risk-adapted monitoring for patients with MGUS
- Impact of monitoring of MGUS is unknown – does it improve survival?
- Population based study of 14,798 patients diagnosed with MM in Sweden (1976-2005)

<table>
<thead>
<tr>
<th></th>
<th>MGUS -&gt; MM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>394</td>
<td>14,404</td>
</tr>
<tr>
<td>Male, %</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>Age at MM diagnosis, median, yrs</td>
<td>73</td>
<td>72</td>
</tr>
<tr>
<td>Overall survival, HR</td>
<td>0.86 (0.77-0.96)</td>
<td>1</td>
</tr>
<tr>
<td>Median OS, yrs</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Survival among M-protein &lt;0.5 g/dL</td>
<td>1.86 (1.13-3.04)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Surveillance of MGUS may be associated with improved survival at MM diagnosis

Patients with low M-protein had inferior survival

Follow-up of MGUS may improve MM outcomes regardless of risk stratification
Metformin reduces progression to MM

- MM always arises from MGUS, yet preventive treatment strategies have not been developed
- Prior studies have shown that IGF-1 and insulin may be important growth factors for MM
- Metformin has multiple actions that may reduce progression to MM
  - Decreases insulin production
  - Induces weight loss
  - Activates AMPK signaling pathway which induces MM cell death
- Metformin reduces the risk of incident cancer in diabetics
- Cohort study of 2,003 non-IgM MGUS patients in the VA
  - 463 were metformin users (defined as at least 4 years)
  - Analyzed duration of metformin use
Metformin reduces progression to MM

Metformin users had a reduced risk of progression to MM - HR 0.47

Metformin use for at least 2 years reduced risk of progression to MM - HR 0.40 – in UK THIN database

Pleiotropic effects of metformin may reduce the risk of progression to MM

Figure: Kaplan-Meier curves for the analytical cohort, stratified by metformin use. Dotted curves are 95% CIs. MGUS = monoclonal gammopathy of undetermined significance.
AMYLOIDOSIS
Fundamental problems in AL

- **Late diagnosis**
  - Organ dysfunction is too severe to withstand effective chemotherapy
  - Patients die of organ dysfunction before they realize the benefits of chemotherapy

- **Cardiac toxicity of native immunoglobulin light chains**

- **Precursor protein production can be reduced with chemotherapy, but...**
  - Clearance of deposited amyloid is slow
  - Clearance of deposited amyloid is often incomplete
Existing therapies all target protein production. There are no therapies to address the toxicity of native light chains or for the existing organ deposits of amyloid.

**Chemotherapy**

- Immunoglobulin light chain

**Doxycycline**

**NEOD001**

**aSAP 11-1F4**

**Organ deposition and dysfunction**

*multistep process of amyloid fibril formation*
Doxycycline improves outcome in AL

- Patients with advanced cardiac AL have a dismal prognosis
- Doxycycline may have cardioprotective effects
  - Interferes with amyloid fibril formation
  - Leads to incomplete or disorganized fibrillar architecture to ease amyloid clearance
  - Interferes and reduces cardiotoxicity of light chains
- Matched case-control study of doxycycline added to chemotherapy in AL performed at UK National Amyloidosis Centre
- Doxycycline 100 mg PO bid with chemotherapy and then continued indefinitely or intolerance
- 103 patients total, 6 with Mayo Stage II, remainder Mayo Stage III
- Median NT-proBNP 4728 (559-37889)
- Regimens: Bortezomib 72%, Thalidomide 23%, Melphalan 5%
### Doxycycline improves outcome in AL

<table>
<thead>
<tr>
<th></th>
<th>Doxycycline</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>30</td>
<td>73</td>
</tr>
<tr>
<td>Hematologic CR/VGPR, %</td>
<td>56/10</td>
<td>35/8</td>
</tr>
<tr>
<td>Cardiac response, %</td>
<td>60</td>
<td>18</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>NR</td>
<td>13</td>
</tr>
<tr>
<td>12 month survival, %</td>
<td>82</td>
<td>53</td>
</tr>
<tr>
<td>24 month survival, %</td>
<td>82</td>
<td>40</td>
</tr>
</tbody>
</table>

![Graph showing survival rates for different stages](image)

Wechalekar ASH 2015
Antibodies to SAP clear amyloid deposits

- All amyloid deposits contain serum amyloid P (SAP) regardless of precursor protein type
- SAP circulates abundantly in the serum
- Depletion of circulating SAP with a small molecule drug (CPHPC) followed by anti-SAP IgG antibody clears amyloid murine model of AA amyloid
- Phase 1 trial of CPHPC with anti-SAP antibody in patients with non-cardiac systemic amyloidosis
- Safety and preliminary evidence of organ responses were assessed
- 16 patients dosed
- No SAEs
- Mild infusion related symptoms to aSAP

# Summary of responses in AL patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg)</th>
<th>Organs</th>
<th>Hematologic status</th>
<th>Improved SAP scan</th>
<th>Evidence of change in amyloid load</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>152</td>
<td>L, S</td>
<td>Stable PR</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>246</td>
<td>L, S, BM, K</td>
<td>CR</td>
<td>Yes</td>
<td>Major liver reduction</td>
</tr>
<tr>
<td>10</td>
<td>400</td>
<td>L, S</td>
<td>Relapse</td>
<td>No</td>
<td>Decreased liver stiffness</td>
</tr>
<tr>
<td>11</td>
<td>650</td>
<td>L, S</td>
<td>Relapse</td>
<td>No</td>
<td>Decreased liver stiffness</td>
</tr>
<tr>
<td>13</td>
<td>650</td>
<td>L, S, K, BM, LN</td>
<td>Relapse</td>
<td>Yes</td>
<td>Major liver and LN response</td>
</tr>
<tr>
<td>14</td>
<td>600</td>
<td>L, S</td>
<td>Stable PR</td>
<td>Yes</td>
<td>Reduction in liver amyloid</td>
</tr>
<tr>
<td>15</td>
<td>600</td>
<td>L, S</td>
<td>Stable PR</td>
<td>No</td>
<td>Decreased ECV</td>
</tr>
<tr>
<td>16</td>
<td>600</td>
<td>L, S</td>
<td>CR</td>
<td>No</td>
<td>Reduction in alk phos</td>
</tr>
</tbody>
</table>

Patient 13
Active clonal disease
5 cm amyloid laden LN
decreased to 1 cm by
day 42
11-1F4 MoAb to amyloid fibrils

- 11-1F4 is a chimeric IgG1 monoclonal antibody which recognizes an epitope on amyloid fibrils
- Phase 1b study in AL to establish dose, assess safety and evaluate for organ response
- A single IV infusion with response assessments over 8 weeks
- 8 patients have been dosed - no SAEs were seen

11-1F4 clears human AL amyloidomas in mice

I-124 labelled 11-1F4 PET/CT detects amyloid deposits
Cardiac Response

Patients with Baseline > 650 pg/mL

3 of 4 patients had evidence of a decreased NT-proBNP at 8 weeks after a single dose of 11-1F4
Summary

*Monoclonal gammopathy of undetermined significance*
- Surveillance of MGUS may improve outcome in MM
- Metformin use may be associated with decreased risk of progression from MGUS to MM

*AL amyloidosis*
- Doxycycline improves survival in advanced cardiac AL amyloidosis
- Therapeutic clearance of amyloid can be induced by monoclonal antibodies to components of amyloid deposits
Current clinical trials at Penn

♦ MGUS and SMM
  • A prospective study of circulating multiple myeloma cells (CMMC) as a biomarker of progression in myeloma precursor states (PI: Weiss, NCT01958528)
  • A randomized phase 2 trial to evaluate three daratumumab dose schedules in smoldering multiple myeloma (PI: Weiss, NCT02316106)

♦ AL amyloidosis – newly diagnosed
  • The VITAL Amyloidosis Study: A phase 3, randomized, multicenter, double-blind, placebo controlled, 2-arm, efficacy and safety study of NEOD001 plus standard of care vs. placebo plus standard of care in subjects with light chain (AL) amyloidosis (PI: Weiss, NCT02312206)

♦ AL amyloidosis – previously treated
  • A safety study of carfilzomib in patients with previously treated systemic light chain amyloidosis (PI: Cohen, NCT01789242)

♦ AL amyloidosis, in hematologic remission with measurable organ dysfunction
  • The PRONTO Study: A phase 2b, randomized study of NEOD001 in patients with persistent cardiac dysfunction (PI: Weiss, NCT01707264)
Penn Amyloidosis Program

- Multi-disciplinary same-day evaluations
- Team
  - **Hematology:** Weiss, Cohen, Vogl, Stadtmauer
  - **Nephrology:** Dember, Hogan
  - **Cardiology:** Drachman, Mathelier (PPMC)
  - **Neurology:** Khella (PPMC)
  - **Pathology:** Palmer
  - **Nurse navigator:** Rummel

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