Secondary immunodeficiency

Applying our knowledge of rare diseases

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Knock outs

- Discovery of basic science pathways
- Determining phenotypes
- Testing drugs
Human knock outs

- Apply our knowledge of rare disease to a wider cohort

- A rare diseases doctor foraying into general medicine.....
20ID— a consequence of successful modern medicine

- Survival rates have dramatically improved over last 20 years
  - Cancer
  - Organ failure / transplant
  - Autoimmune
  - Auto-inflammatory disease

- Increasingly necessary to manage the survival
The prevalence of 2°ID

• Pneumonia remains the 5th highest cause of death in the UK
• Infection accounts for 11% (5.3 million) of all bed days

• HIV – 100,000 individuals in the UK
• Haematological malignancy - 30,000 new cases a year

• Chronic disease – 17.5 million individuals in the UK
  • Arthritis - 8 million
  • Moderate to severe chronic kidney disease - 5 million
  • Chronic lung disease - 5.2 million
  • Diabetes -1.3 million

• Age over 65 years - 9.2 million in the UK
  • associated with an increased infection rate and more severe outcome
So what is left to do in this research field?

1. Recognise the risk of $2^0\text{ID}$

2. Diagnose the $2^0\text{ID}$

3. Manage the $2^0\text{ID}$
Recognising the risk

- **Rituximab**
  - 1/3 low immunoglobulins (Igs) after 5 cycles
  - warning signs from early licensing for lymphoma
  - Immunologists started to be referred patients who don’t reconstitute their B cells and their Igs ↓↓↓

UHB cohort on Ig replacement - % of 2ID patients with prior immunosuppression

- 74%
- 6%
- 10%
- 7%
- 3%
Looking for antibody deficiency - calculated globulin

- Total protein – albumin = globulin
- 8 days of secondary and primary care liver function tests
- 64 out of 7481 (0.86%) total patients had low globulins
Chemotherapy is immunosuppressive but how immunosuppressive?

- Profoundly low lymphocytes post high dose melphalan in myeloma
- And for how long........?
- Not just neutropenic sepsis

![Graph showing cell number x 10^9 for different cell types in the TEAMM trial with n=107]
Diagnosing 2\textsuperscript{0}ID

- Chronic lymphocytic leukaemia
- Antibody deficiency can be found in >1/3 of watch and wait patients
- Should focus be on managing the immunodeficiency?

<table>
<thead>
<tr>
<th>CLL Subjects</th>
<th>Stage A Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>35</td>
<td>21</td>
</tr>
<tr>
<td>Age (median, IQR)</td>
<td>71 (IQR 65-76)</td>
<td>74 (IQR 65-81)</td>
</tr>
</tbody>
</table>

**Laboratory parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stage A Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG &lt;6 g/l, n= (%)</td>
<td>10 (29%)</td>
<td>12 (57%)</td>
</tr>
<tr>
<td>IgM &lt;0.5 g/l, n= (%)</td>
<td>27 (77%)</td>
<td>14 (66%)</td>
</tr>
<tr>
<td>IgA &lt;0.8 g/l, n= (%)</td>
<td>14 (40%)</td>
<td>11 (52%)</td>
</tr>
</tbody>
</table>

**Infection history**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stage A Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one documented infection, n= (%)</td>
<td>17 (49%)</td>
<td>14 (67%)</td>
</tr>
<tr>
<td>At least one infection admission, n= (%)</td>
<td>7 (20%)</td>
<td>8 (38%)</td>
</tr>
</tbody>
</table>

Parry et al
ANCA associated vasculitis

- Often be a profound combined cellular and humoral deficiency
- Long lasting even on reducing immunosuppression
- Results in varied, frequent and severe infection

**Lymphocyte subset numbers in ANCA positive vasculitis patients**

<table>
<thead>
<tr>
<th></th>
<th>Lymphs</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD19</th>
<th>CD16/56</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1000</td>
<td>2000</td>
<td>3000</td>
<td>4000</td>
<td>5000</td>
<td>6000</td>
</tr>
</tbody>
</table>

Error bars indicate mean ± 95% CI

**IgG level**

- Control group

- Often be a profound combined cellular and humoral deficiency
- Long lasting even on reducing immunosuppression
- Results in varied, frequent and severe infection

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Morgan / Harper
Immune studies in cancer patients

Immune phenotyping may aid:
1. Diagnosis
2. Side effect profile (check points)
3. Prognosis

? immunodeficiency increases risk of cancer

V

Cancer causes immunodeficiency

Merkel cell carcinoma (Neil Stevens)

32% with low B cells

Interesting NKT cell populations
Immune competence predicts response?

- Functional antibodies against vaccine preventable disease
- Responders have more antibodies at presentation

Myeloma IX data - Drayson
3. Managing the immunodeficiency

• Can the immunodeficiency be reversed
  – Treat the underlying cause
  – Reduce immunosuppression

• Reduce the risk of infection
  – Vaccination
  – Prophylactic antibiotics
  – Immunoglobulin
Vaccinating in 2010

- Conjugate versus polysaccharide vaccination in HIV
- HIV-infected patients mount a more immunogenic response to: Prevenar-13 (54%) v Pneumovax-23 (33%)

Clinical impact:
Expected respiratory admissions reduced by 37% following the vaccination schedule

Slaney / Faustini

Whitelegg et al
Vaccination in ANCA vasculitis

- It can be hard to protect the most vulnerable
- The more profound the immunodeficiency the weaker the response to vaccine

- 92 patients with ANCA associated systemic vasculitis
- Vaccinated with Prevnar, Men ACWY polysaccharide, menitorix

Morgan / Harper
Applying rare disease philosophy

- $2^0$ID patients often require coordinated multi-disciplinary

- Operating within a sparse evidence base

- Taken knowledge of rare disease and applied to a wider health care problem
2^{0}\text{ID} - a \text{ conundrum}