It was the best of times, it was the worst of times

The role of Rituximab in the treatment of Autoimmune Disease

Dr Sarah Sasson
HIV/Immunology Registrar
HIV, Immunology and Infectious Diseases Department,
St Vincent’s Hospital

Inspiration for this talk...

Introduction to Rituximab (RTX)

- Chimeric anti-CD20 mAb
- Approved for treatment of B-cell tumors in 1997
- Approved for the treatment of RA in 2006
  - Interestingly RA previously thought to be a largely T-cell mediated disease

Introduction to Rituximab

- CD20 is associated with the B-cell receptor and is thought to be an ion/Ca2+ channel.
- Binding a mAb to CD20 can lead to apoptosis, homotypic aggregation and complement activation

Introduction to Rituximab

- CD20 is expressed on the majority of mature and malignant B-cells
- CD20 is NOT expressed on plasma cells

Introduction to Rituximab

- Currently it is believed that antibody dependent cell-mediated cytotoxicity (ADCC) is the major mechanism by which RTX facilitates B-cell depletion
- In 1999 Protheroe et al reported regression of RA in a patient receiving RTX for concurrent B-NHL. This provided the rationale for treatment of other patients with RA and other autoimmune disease.
- Ongoing off-label use of RTX in trials investigating the role of B-cell depletion in autoimmune disease.
The role of B-cells in Autoimmunity

- Production of autoantibody and immune complexes
- Antigen presentation to T-cells
- Inflammatory cytokine production
- Neo-organogenesis at sites of disease eg synovium, salivary glands, kidneys, ventricular meningeal compartment

Rituximab: Proposed mechanisms of action

Rituximab in RA

- 3 controlled clinical trials have demonstrated the efficacy of Rituximab in the treatment of RA including in those who had failed Infliximab
- Dose 1g Day 1 and Day 14

Rituximab in Sjogrens Syndrome (SS)

- Similar to RA
  - 70% RF+
  - Inflammatory arthritis common
  - Some RA patients have xerostomia and xerophthalmia
- Initial reports: 2 patients treated with RTX for marginal zone lymphoma had improvement in SS symptoms

Rituximab in Sjogrens Syndrome (SS)

- Around 66 patients have been reportedly tx for SS with RTX with overall response rate 44-83%
- Generally associated with reductions in RF but not SSA/SSB
- Level of evidence limited by small sample size, design limitations (some retrospective), mixed populations of primary and secondary SS
Significant improvement in fatigue, social functioning and depression in patients treated with RTX

No significant difference in autoantibody levels, Schirmer's test or salivary flow

Not currently licensed for use in Aus

Mean fatigue visual analogue scale at baseline and 6 months.

P<0.001

Total of 192 patients have been treated in 12 smaller open label studies

Overall response rate 78-90%

Especially beneficial in patients with renal or neuropsychiatric involvement

Clinical improvement associated with decreased levels of anti-dsDNA

Rituximab in SS

Rituximab in SLE

Mean fatigue visual analogue scale at baseline and 6 months.

P<0.001

Rituximab in SLE

Rituximab in SLE

Rituximab in SLE

Rituximab in SLE

Rituximab in SLE

Rituximab in SLE

Rituximab in SLE

Rituximab in SLE

Rituximab in SLE

Rituximab in SLE

Rituximab in SLE

Rituximab in SS

Rituximab in SLE

Rituximab in mixed cryoglobulinaemia (MC) aim of RTX is to reduce IgM RF synthesis and reduce clones that sustain the disease

74 patients have been treated with a response rate of 80-93% and a relapse rate of 39%

Improvement found in skin lesions, neuropathy, arthralgia and renal function.

Reduction in cryocrit, RF and normalisation of C4

Of concern HCV VL increased in responders vs non-responders
RTX and ANCA+ Vasculidities

- Treatment has been reported in 96 pts with ANCA vasculidities
- Response rate close to 90% in most studies
- Symptoms related to small vessel vasculitis and glomerulonephritis appear to respond more quickly
- Granulomatous disease was slower to respond
- The majority of responders revert to having a negative ANCA

Rituximab in Haematological Disorders

- Overall 62.5% response rate in ITP
  - Younger age and female sex predicted outcome
  - Response to children comparable to that of adults—therefore a valid alternate to splenectomy

- In idiopathic AIHA 10% of patients are refractory to other treatments
- 65 patients have been reportedly treated with RTX with a response rate of 40-100%

Rituximab in MS

- Potential role of B-cells in the pathogenesis of MS suggested by:
  - Clonal B-cells in plaques
  - Oligoclonal bands in CSF
  - Anti myelin oligodendrocyte glycoprotein Ab in lesions
  - Ectopic lymphoid follicles in intrameningeal spaces

- HERMES phase II DBPC trial of RTX in relapsing-remitting MS
  - 104 pts randomized to received 1g RTX/placebo on Day 1 and 15 and followed for 48 weeks
  - Primary endpoint was number of GAD enhancing lesions on MRI
Rituximab in MS
- Patients receiving RTX had reduced total and new number of plaques and decreased clinical relapses
- RTX associated with a higher number of mild-moderate adverse events
- Results not replicated in primary progressive disease

Hausler et al. NEJM 2008

Rituximab in Dermato/Polymyositis
- Few studies in this area approx 30 patients treated
  - Some improvement in muscle strength
  - Only marginal benefit in cutaneous symptoms
  - Short term efficacy
  - No clear optimal dose

Persa et al. J Int Med 2010

Rituximab in blistering skin disease
- Pemphigus vulgaris (PV) is a rare autoimmune blistering disease that involves skin and mucous membranes.
- AutoAb target desmoglein 1 and 3
- In one study RTX was combined with IVIG treatment
  - Induced rapid long lasting improvements
  - IgG4 levels became undetectable in 4.6m
  - Total anti DSG3 titres also dropped
- Randomised Placebo-Controlled Double blind studies are pending


Rituximab: Adverse events
- B-cell depletion post RTX often lasts >6m followed by process of repopulation
- Can induce neutropenia and thrombocytopaenia
- Immunoglobulins do not fall below normal levels in the majority of patients however the risk of hypogammaglobulinemia increases with increased doses.
- Early vaccination 4-8 weeks after RTX administration resulted in decreased Ab production to influenza compared with MTX or pt vaccinated later 6-20m post RTX
- The presence of pre-existing memory and plasma cells also associated with higher Ab titres (plasma cells not sensitive to RTX)
### Rituximab: Adverse events

- Overall increased risk of general infections have not been consistently shown
- Pre screen for TB, HBV, HCV

<table>
<thead>
<tr>
<th>Rituximab: Adverse events</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of HBV reactivation is 20-50% among HBsAg having chemo or immunosuppressive therapy with a mortality of 10-40%</td>
<td></td>
</tr>
<tr>
<td>In a study of 46 pts with B-NHL 21 receiving R-CHOP 5 reactivated HBV and 1 died and 25 of those receiving chop alone had 0 reactivations</td>
<td></td>
</tr>
<tr>
<td>Current guidelines</td>
<td></td>
</tr>
<tr>
<td>Prescreening for HBV</td>
<td></td>
</tr>
<tr>
<td>Treatment with lamivudine for HBsAg+ patients continued up to 6m post RTX cessation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many questions remain</td>
<td></td>
</tr>
<tr>
<td>When should RTX be commenced?</td>
<td></td>
</tr>
<tr>
<td>What is the optimum dose?</td>
<td></td>
</tr>
<tr>
<td>What is the optimum schedule?</td>
<td></td>
</tr>
<tr>
<td>What precautions should be taken?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>The licensing of RTX for use in RA has opened the door for a possible therapeutic role in other autoimmune diseases</td>
<td></td>
</tr>
<tr>
<td>There is emerging data in case series and smaller scale studies that RTX is effective in the treatment of SS SLE, MC, WG, ITP, AIHA, relapsing and remitting MS and PV</td>
<td></td>
</tr>
<tr>
<td>The level of evidence for the majority of these is not robust</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Future directions: development of a fully humanised anti CD20 mAB</td>
<td></td>
</tr>
<tr>
<td>Overall it is likely that RTX would be a useful addition to the armament for the treatment of such diseases, the challenge remains in</td>
<td></td>
</tr>
<tr>
<td>Completing PRDBC studies demonstrating effectiveness in low prevalence diseases that present heterogeneously</td>
<td></td>
</tr>
<tr>
<td>Determining objective endpoints for many of the diseases</td>
<td></td>
</tr>
<tr>
<td>Cost/benefit analysis for what remains a very expensive drug being used for less common, chronic, non-fatal diseases</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

“Rituximab seems to be good in real life, but bad in controlled trials”

Questions?

Question for Westmead: what are your experiences in treating autoimmune diseases with Rituximab?