Monoclonal Antibodies

Assessing the handling risks

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- 2007 team of pharmacists & nurses reviewed available literature in response to concerns over the handling of MABs.
- Published paper has been challenged as over estimating the risks.
- Resulting correspondence and reference source published in 2008 has made more information available.

This presentation:

- Reviews the existing approach to assessing the handling risks.
- Discusses the above approach from a further understanding of the underlying science.
- Reviews potential risks & mitigating factors

What are the issues?

- MABs are very active biological agents.
- Precedent set by exposure to cytotoxic agents.
- Minimal guidance from existing publications
- A lack of knowledge of underlying science of MABs and protein therapeutics amongst healthcare staff.

The potential exposure risk?

- Potential risk MABs present to healthcare staff is;
  - Chronic long term exposure to:
  - Very active biological agents.
  - Handling multiple agents.
  - Potential risk from aerosol inhalation.

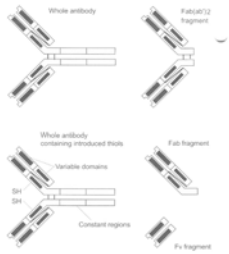
Existing approach

- MABs are proteins – therefore have immunogenic potential.
- Risks identified from side effects arising from therapeutic use.
- However this extrapolates from:
  - Therapeutic dose levels.
  - Does not distinguish between serious reactions that either from an intrinsic MAB property or arising from the disease state.
    - Does not distinguish between the cellular level (MAB) against the molecular (small molecule therapy).
    - Risks have therefore been overestimated?

On names

- momab = 100% murine
- ximab = 60 – 70% human
- zumab = 90 to 95% human
- mumab = 100% human

MAB diagram (Roberts G, Eur J Pharm Sci, 1997, p21)



Immunogenicity of MABs

- Murine
  - Classical response,
  - 1st/2nd dose,
  - Formation of neutralising antibodies,
  - Re-challenge leads to booster reaction (memory),
  - Potentially severe reactions,
  - Humanise – expect reduced immunogenicity.

Immunogenicity - reviewed

- Human forms do exhibit immunogenicity – e.g. daclizumab with a 9% (SPC) incidence of human-anti-human antibody formation.
- Breaking of B cell tolerance;
  - 6-12 months chronic treatment,
  - Binding antibodies – no biologic effect,
  - No memory,
  - Disappear on stopping treatment,
  - How this happens & significance unclear.

Immunogenicity - causes

- However most MABs are immunogenic to greater or lesser degree.
- Intrinsic properties may contribute;
  - direct activation of T cells,
  - boost immune response by macrophage activation
  - binding to cell-bound antigens leads to higher antibody levels than circulating targets.
- Purity of preparation, formulation & formation of aggregates are all important.
- Most likely effect is loss of efficacy.

Intrinsic properties of MABs

- Profoundly immunosuppressant;
  - Act through complement –dependent cytotoxicity (CDC) or antibody – dependent cellular cyctoxicity (ADCC).
  - Rituximab – complete depletion of circulating B cells with in 2 weeks

Intrinsic properties

- Alemtuzumab – CD52 widely distributed. Triggers complement dependent cytotoxicity. 90% injection reactions, sever prolonged lymphopenia.
- Cetuximab & Panitumumab – anti EGFR – affect skin integrity, severe skin reactions

Risk factors

- Cytotoxic & immunosuppressive.
- Profound immunosuppresson – opportunistic infections & development of malignancy.
- All may give rise to antibodies.
- Lower, episodic dosing more immunogenic than high doses.
- Long half life – particularly humanised, days/weeks.

Risk factors continued

- Specific targets – but may be expressed in several tissues.
- Chronic long term exposure.
- Multiple agents.
- Potential absorption through lung ?
- Anti-EGFR MABs effect skin integrity & manifest severe skin toxicities.

Mitigating factors

- Very low dose – rapidly cleared from body.
- Immunogenicity not classic type – binding antibodies, not neutralising, no memory.
- Cell mediated toxicity – not at nuclear level.
- Up to 10 years in widespread use – so far one anecdotal verbal report of severe reaction from occupational exposure in healthcare staff.

Conclusion – is there a handling risk?

- Have no data on chronic low grade exposure.
- Not being looked for?
- High molecular weight, low dose exposure – mitigated by simple measures of wearing gloves and face masks.
- Left with impression of profoundly active agents – would want to be cautious in the potential exposure of healthcare staff.