Development and challenges to monoclonal antibodies for passive immunization

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A brief history of serum derived passive immunization


- Widely used in first half of 20th century: eg. Measles, polio, pneumococcus, Hib, 1918 pandemic convalescent plasma.

- Use declined with vaccines and the discovery of antibiotics.

- But still used today for: RIG, DAT, TIG, BIG, HepA, HepB, HepC, VIG, VZIG…..etc. (Equine & Human)
Opportunities for MAbs

- Replacement of blood-derived Igs (supply issues)
- Emerging infections
- Pandemics
- Function quicker than active vaccines
- Where vaccines are not available
- Antimicrobial resistance (e.g. MSRA)
- Opportunistic infections, immuno-suppressed
- Hospital acquired infections
- Bio-defence (i.e. anthrax)
State of development: mAbs for infectious diseases

- **5 Licensed:**
  - **RSV:** Synagis (palivizumab) by MedImmune, since late 1990s
  - **Anthrax:** Abthrax (raxibacumab) by GSK & Anthim (obiltoxaximab) by Elusys therapeutics – both licensed under FDA animal rule in 2012 and 2016
  - **Rabies:** RMAb (HuMAb17C7) by SII, licensed in India in 2016, not yet launched
  - **Clostridium difficile** (recurrent): Zinplava (Bezlotoxumab) by Merck, FDA approved in October 2016

- **At least 38 in active clinical development** for 13 diseases:
  - botulism, C difficile, Ebola, hep B, hep C, Hendra virus, HSV, HIV, influenza, Pseudomonas aeruginosa, rabies, RSV, Staph aureus

- Numerous others in preclinical development…
Challenges

- **General:**
  - Short duration of protection
  - Improving the mAb – longer ½ life, higher affinity
  - Route of administration (IV not ideal for LICs)

- **Defining the purpose & endpoint & outcome measures**
  - Pre- or post exposure (at what time point?), treatment?
  - Reduction in transmission, infection, severe illness, hospitalization?

- **Economic viability**
  - An antibody only works against a single disease target. If this disease is rare, or episodic is there a business model to support the continued production? R&D costs when market is unsure.
  - Product end-price will depend on the amount of mAb needed, may not be cost effective in some cases
Challenges

- Demonstrating efficacy in clinical trials for rare/emerging infections
  - Small number of patients, unpredictable outbreaks, high fatality associated with the ethical challenges of conducting RCTs
  - Alternative regulatory pathways needed, robust animal models

- Where blood derived Igs exist, such as for rabies, RCTs are ethically challenging (informed consent for a fatal disease?)
  - Switching from approved polyclonal to new mAb?

- Breadth of protection, pathogen escape
  - Neutralization across different genotypes? Polyclonal serum targeted multiple sites – will pathogens develop escape mutants to monoclonal products?
The FDA animal rule

- When efficacy cannot be tested in clinical trials for ethical or practical reasons

- Animal models can replace pivotal human efficacy studies
  - Well characterized non-human models of the disease
  - Comparable pathophysiology of animal model of the disease to the human disease
  - Justification of challenge dose and route of challenge, timing for intervention, etc.

- Human studies to confirm safety and compare PK in animal model with PK in humans

- Case by case basis
Example: Anthrax & the FDA animal rule

Raxibacumab was approved by FDA in 2012 based on the "Animal Rule"\(^1\)

- 1 NHP and 3 rabbit challenge studies to evaluate efficacy
- Safety and PK evaluated in 326 healthy human volunteers.

1. FDA news release 14 Dec 2012
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm332341.htm
Cost-effectiveness & access considerations

- Current production costs ~$US 100 per gram of mAbs – if several grams are needed…?  

- Targeted use in high-risk individuals may present a cost-effective strategy.

- No WHO Prequalification yet (a GAVI requirement)
  
  - A new pilot project on biosimilar mAbs launched in May (2 oncology mAbs)

- SAGE recommendations?

- Route of administration – IM preferred to IV
Example: influenza mAbs

- Therapeutic vs prophylactic use (preclinical & clinical design will differ)
- Market for seasonal influenza (therapeutic)
- Pandemic use:
  - Vaccines will take 4-6 months following declaration of pandemic, first line response?
  - Stockpiling?
- 8 products in clinical development
  - Reported to be broadly protective across all 18 subtypes of influenza A
  - All being evaluated as intravenous infusion
  - Dosing from 1 to 50 mg/kg (for 60 kg this would mean 3g, CoG $300)
  - Comparison to antivirals?
Needs

- Alternative clinical trial design
  - Especially for outbreak settings and diseases with high case fatality

- Collaboration between regulatory agencies
  - If trials are to take place in multiple countries

- Improved and robust animal models
  - When human efficacy data will be difficult to gather

- Standardized clinical endpoints

- International reference standards and bio-assays
Question for PDVAC

- What role can/should WHO-IVR play?
  - Landscape review & feasibility assessment by pathogen?
  - PPC for LMICs – i.e IM versus IV, cost considerations