Pharmacokinetics of Biologics


MONOCLONAL ANTIBODIES

- Immunoglobulin molecules that are secreted form a population of identical cells. Monoclonal = monospecific. Single epitope produced by single type of immune cell
- Good:
  - Highly potent
  - Highly specific
  - Tailored therapies
- Bad:
  - Complex
  - Difficult characterization
  - Expensive
- Used as:
  - Immunotoxic therapeutic agents
  - Cytotoxic agents
  - Agents that alter cell function
  - Antibody directed targeted drug delivery

TYPES OF MONOCLONAL ANTIBODIES

- Murine = completely mouse
- Chimeric = mouse variable region
- Humanized = human and mouse variable region
- Completely human \( \rightarrow \) largest \( t_{1/2} \) \( \rightarrow \) less chance of hypersensitivity
  - Highest potency
- Most administered parenterally \( \rightarrow \) influences absorption

PK PARAMETERS OF MONOCLONAL ANTIBODIES

- Reticuloendothelial system (RES) degradation (NOT by CYP enzymes)
- Absorption: the larger the size, the longer it lasts in lymph, the longer it circulates throughout the body
  - Route: IV, SC, IM
  - Duration of absorption is hours to days
  - Cmax at 1-8 days
• Distribution determined by:
  o Rate of extravasation into tissue
  o Rate of distribution into tissue
  o Rate of antibody binding in tissue
  o Rate of elimination from the tissue

• Metabolism – biologics act like other proteins in your body
  o Metabolized by intracellular catabolism following fluid phase or receptor mediated endocytosis

• Elimination: t_{1/2} depends on the source
  o Want a large t_{1/2} and large % already circulating in the body → use IgG1
  o Soluble → removal by RES → linear kinetics (dose-independent)
  o Membrane-bound = elimination by binding to the target (non-linear, dose dependent)
  o Low [mAb] = short t_{1/2} = all antibody will bind antigen and be eliminated
  o High [mAb] = long t_{1/2} = still have mAb circulating and recycling even when all antigen is bound

FCRN INTERACTION

• FcRN = neonatal receptor that interacts with monoclonal antibody to enhance circulation
  o Recycles IgG and maintains humoral immunity
  o Mouse IgG can’t be recycled in humans → shorter half life in humans

• Expressed in all tissues but highest in vascular endothelium
• IgG finds it’s FcRN at acidic pH and is taken into the endosome (acidic) so can bind to FcRN
  o Once endosome in recycling process, can release IgG to physiologic pH

MONOCLONAL ANTIBODIES SUMMARY

• mAbs are a growing class of drugs
• mAbs make up the largest market of biologics
• Injection mAbs allow circulation for hrs-days (depends on origin)
• mAb distribution is largely based on size as well as antigen
• mAb metabolism is independent of CYP
• mAb elimination via RES or receptor mediated mechanisms
• Potent and specific, but expensive, hard to scale up, immunogenicity issues
• Large and expanding future for biologic drugs