Off-target toxicity – a regulator's view

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The views presented here are my own and do not necessarily reflect the views of the Paul-Ehrlich-Institut.

Off-target toxicity – does it occur ?

- monoclonal antibodies are highly specific

- yes, off-target toxicity is observed, but is a rare event (see references)

  - 5 cases provided by EBE
    mAbs associated with off-target platelet activation, thrombocytopenia and/or anemia in non-clinical studies
    cause for this off-target toxicity and relevance to humans not always clear

  - cross-reactivity of a humanized anti-FGFR4 mAb with murine complement C3 associated with rapid clearance

  - cross-reactivity of a humanized anti-Aß mAb with cynomolgus fibrinogen, associated with fast elimination

- off-target toxicity observed for newly developed mAbs

Off-target toxicity to be expected for biosimilar mAbs?

- biosimilar mAb designed and produced to be similar to reference mAb
- identical amino acid sequence, no difference in antigen binding site or Ig framework
- similarity is controlled by thorough characterization at the quality level, nevertheless, subtle quality differences may be expected
- in addition, similarity is controlled by characterisation of all functional aspects of the molecule by sensitive and quantitative in vitro assay functional differences should not be present
- given the similarity to the reference product differences in toxicity profile are not expected no reason to expect off-target toxicity by the biosimilar

Off-target toxicity by biosimilar mAbs

- experience is limited
- data from clinical trial applications for 5 biosimilar mAbs
  all with comparative toxicology studies
- only the known effects were observed
  so far, no evidence for off-target toxicity

Off-target toxicity – how to detect it?

- off-target binding:
  - immunohistochemistry staining of human tissues
    comparison biosimilar vs. reference mAb
    sensitivity/suitability of the method is questionable

  - protein biochip analysis
    predicitivity of off-target binding to proteins on chip for off-target binding in vivo is unclear

- Off-target effects:
  - non-clinical toxicology study
    not sensitive enough to detect subtle effects
    major effects are not expected

  - clinical trial

References

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