ADA Drug Tolerance – Why and when ?

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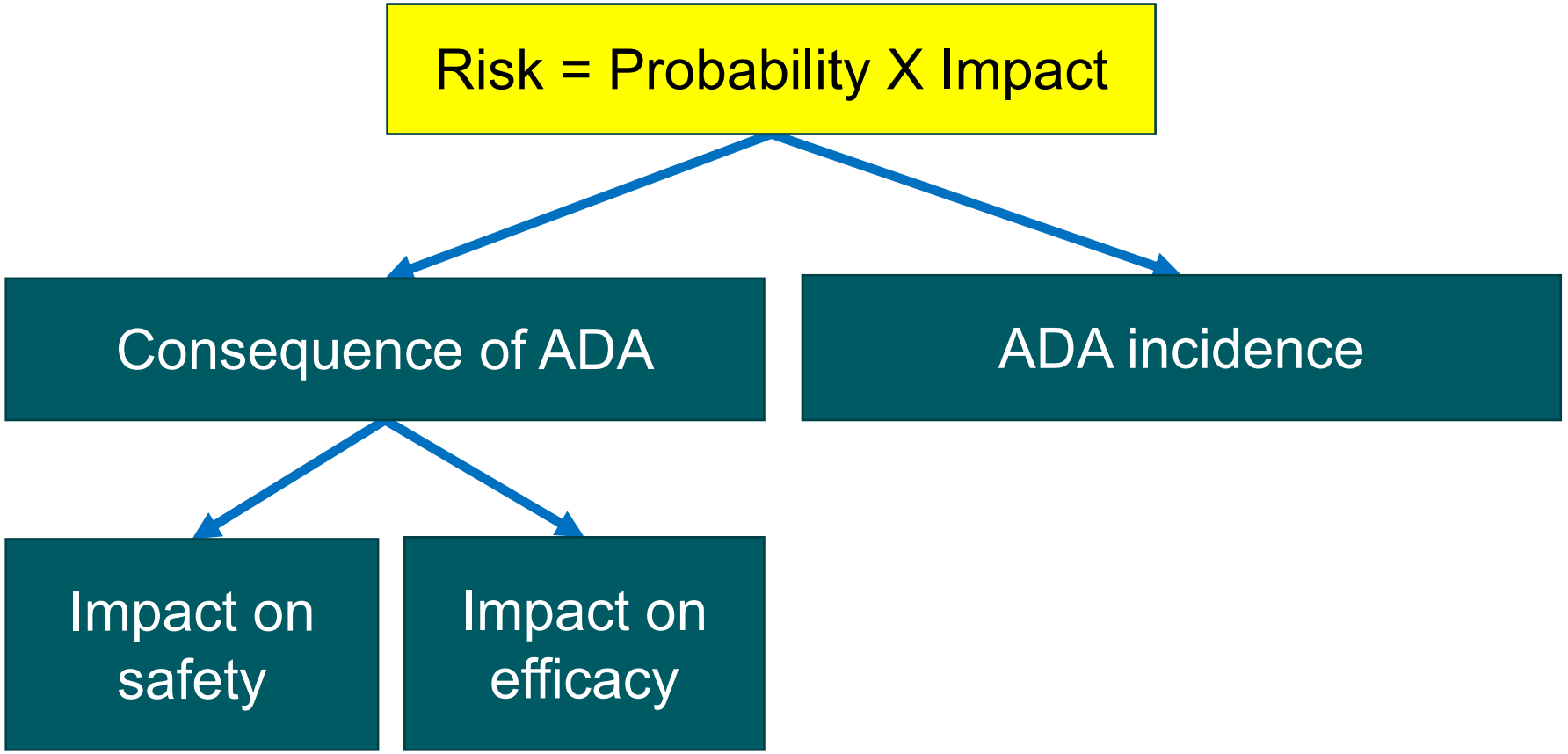
Immunogenicity Risk



Modalities

- Cytokines, Hormones
- Non-protein biologicals (e.g. oligos)
- Monoclonal antibodies
- Bi-/Tri-specifics
- Vehicles (e.g. AAV, LNP)
- Cellular Therapeutics (CAR-T, CAR-NK)

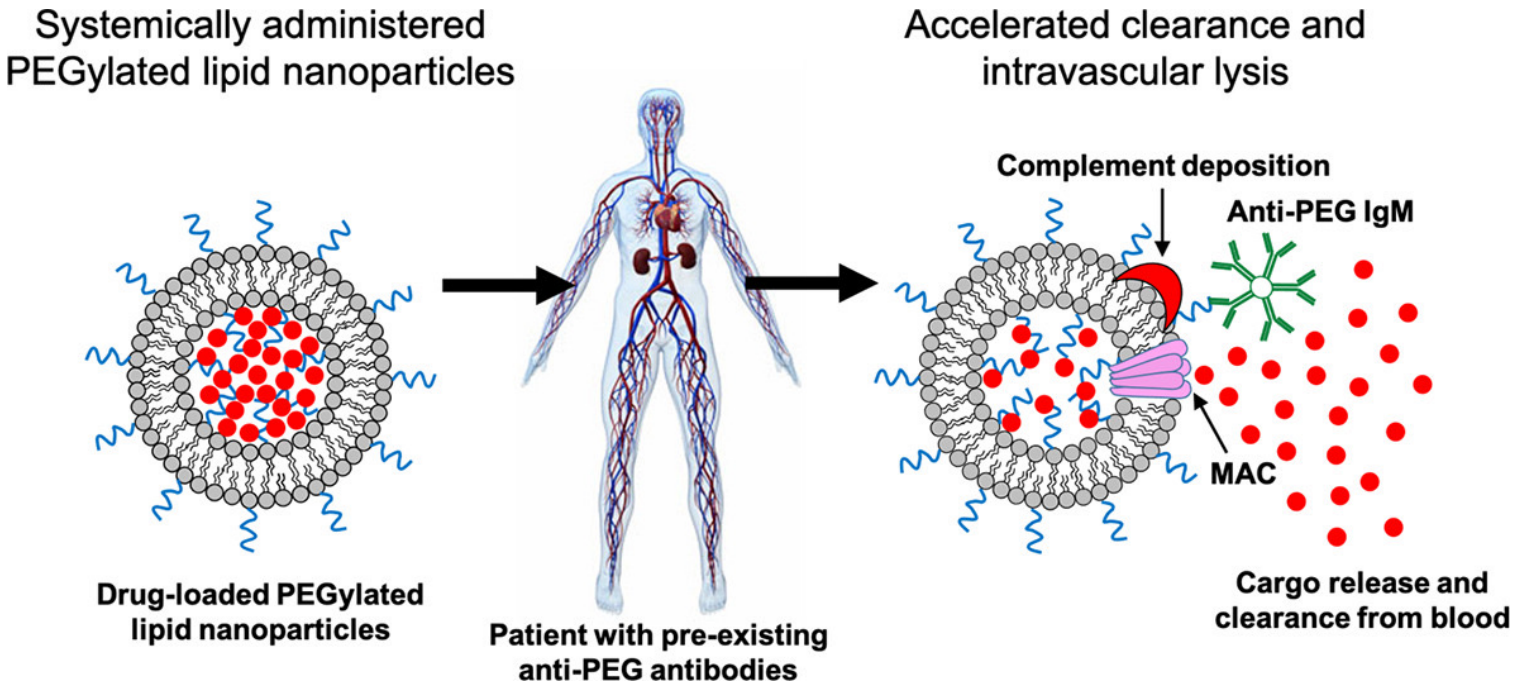
DT assessment at different tiers

- Screening assay
- Confirmatory assay
- Titer assay
- Characterization assays
  - Domain specificity
  - NAB-CLBA
  - NAB-CBA

Why is the assessment of Drug Tolerance needed?

1. Why are false negative results in the presence of the drug a concern ?
2. Is there an impact of ADA on efficacy or PK ?
3. Is there a safety concern, e.g. complement activation ?

Innate Immune Response



Senti ME et al. J Controlled Release (2022)

How is the Drug Tolerance to be assessed?

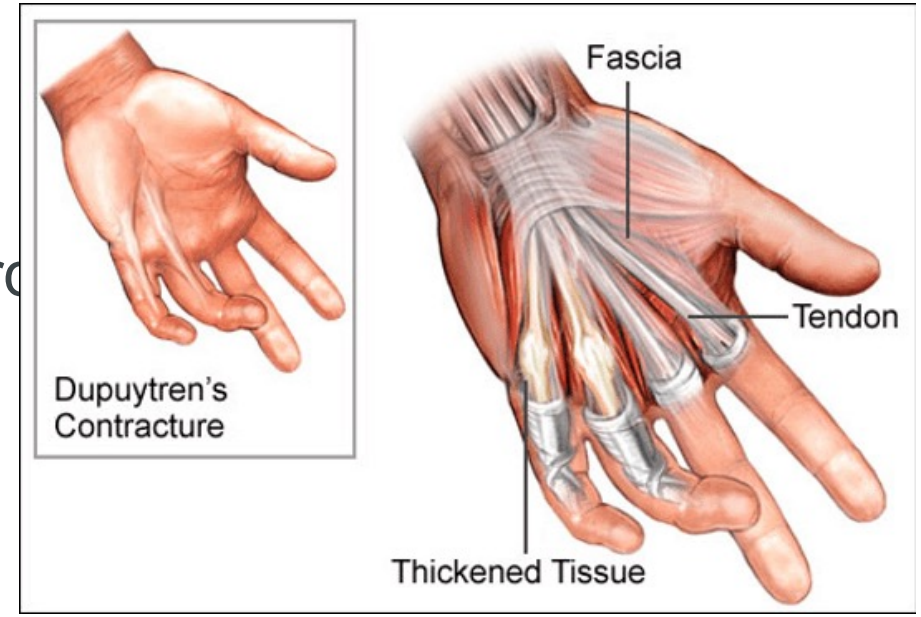
1. Just wait
2. Increase MRD
3. Heating
4. Acid dissociation
5. ACE, SPEAD, PandA etc
6. Spiking experiments at 100 ng/mL ADA and not at LPC

Sample Timing

1. Half-life time of some modalities are short
    a. Insulin 10 min
    b. Interleukin 15 min
    c. Erythropoietin 6 hours
2. ADA sampling at 5 x $t_{1/2}$
3. No drug tolerance assessment needed

Topical Administration

1. Collagenase clostridium histolyticum (Xiapex)
2. Indicated for the treatment of Dupuytren's contracture in adult patients with a palpable cord
3. Administered into the Dupuytren's cord
4. Immunogenicity:
    a) After first injection: up to 92%
    b) After a third or fourth injection: 100% subjects developed ADA to both AUX-I and AUX-II



Increase MRD

- Increase of MRD has an impact on sensitivity
- If the sensitivity at MRD2 is 10 ng/mL, increase of MRD20 leads to a still acceptable sensitivity of 100 ng/mL
- The drug is diluted accordingly and possibly no action is needed.

ADA level

1. FDA guidance recommends a sensitivity of 100 ng/mL
2. Limited clinical relevance at this level
3. Spike experiments at 100 ng/mL or 250 ng/mL may be sufficient
4. Justification needed

AD, SPEAD, ACE, PandA

1. All good and acceptable methods
2. Define the MRD
3. Impacted recovery ADA might be a concern

How to control the techniques?

1. Efficiency of acid dissociation of immune complexes
2. Destruction of drug
3. Destruction of ADA
4. Destruction of functionality

DT for NAB assays

1. Often not assessed
2. Challenging for CBA NAB

Concluding keys

- Safety & Efficacy is key for the Immunogenicity Assessment
- Clinical relevance is key for the IG evaluation
- Most important key is being mindful to assess the drug tolerance