H E S I

Developmental Immunotoxicity Testing of Pharmaceuticals

Regulatory Perspective

Beatriz Silva Lima
iMED-Lisbon University
CHMP-Safety Working Party Chair

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Disclaimer

- The views presented in this session are of the responsibility of the Author and Not of the Institutions She Belongs.

Current Regulatory Perception

Potential Immunotoxicity is systematically addressed following ICH S8 principles and strategies:

- detection of signals in repeated dose studies

-further studies in case of positive signals

-Performed in adult animals

In PIPs concerns regarding DIT are increasingly emerging.

Current Regulatory Perception

Concerns on DIT identified mainly with Biologics Particularly Mabs.

- -Poor description in EPARS
- -More apparent in
  - -Scientific Advice
  - -PIPs

Case: Raptiva (2004)

- Efalizumab,
- rHMab (IgG1) with immunomodulatory properties.
- binds specifically to the CD11a subunit of LFA-1 (a leukocyte cell surface protein)
- inhibits the binding of LFA-1 to ICAM-1, -2, and -3 (intercellular adhesion molecules 1, 2, and 3)
- Interfering with lymphocyte adhesion to other cell types.

Case:Raptiva

- Approved indication: treatment of adult patients with moderate to severe chronic plaque psoriasis

- Nonresponders, or with contraindication, or intolerant to other systemic therapies incl. cyclosporine, methotrexate and PUVA.

Case: Raptiva

- Secondary Pharmacodynamics:

  Inhibition of both the humoral response to some antigens and the cell-mediated response, eg:

  -primary antibody-response in NHP to tetanus toxoid

  -primary and secondary response in mice to sheep red blood cells

  -inhibition of the delayed type hypersensitivity (DTH) in mice.

Case: Raptiva

Reprotoxicity: Murine Embryofetal Study

- MuM17 crossed the placenta of pregnant mice.
- No treatment-related effects observed with muM17 in mice up to 30 mg/kg/week.

Case: Raptiva

Peri/Postnatal Reprotox with muM17:

F1 Mice up to > W11 Age, nonsignificant at W25 :

- ↑ spleen weight (PD)
- ↓ Ab forming cell response to SRBC (↓ T-cell immunity)
- relative ↑ in CD4+ cells and ↓ in CD8+ cells.
- ↓ primary Ab response
- Cross-reactivity with other cells of immune system, eg
  - glial cells
  - stromal cell

Case: Raptiva

- MA Suspended due to increased incidence of PML

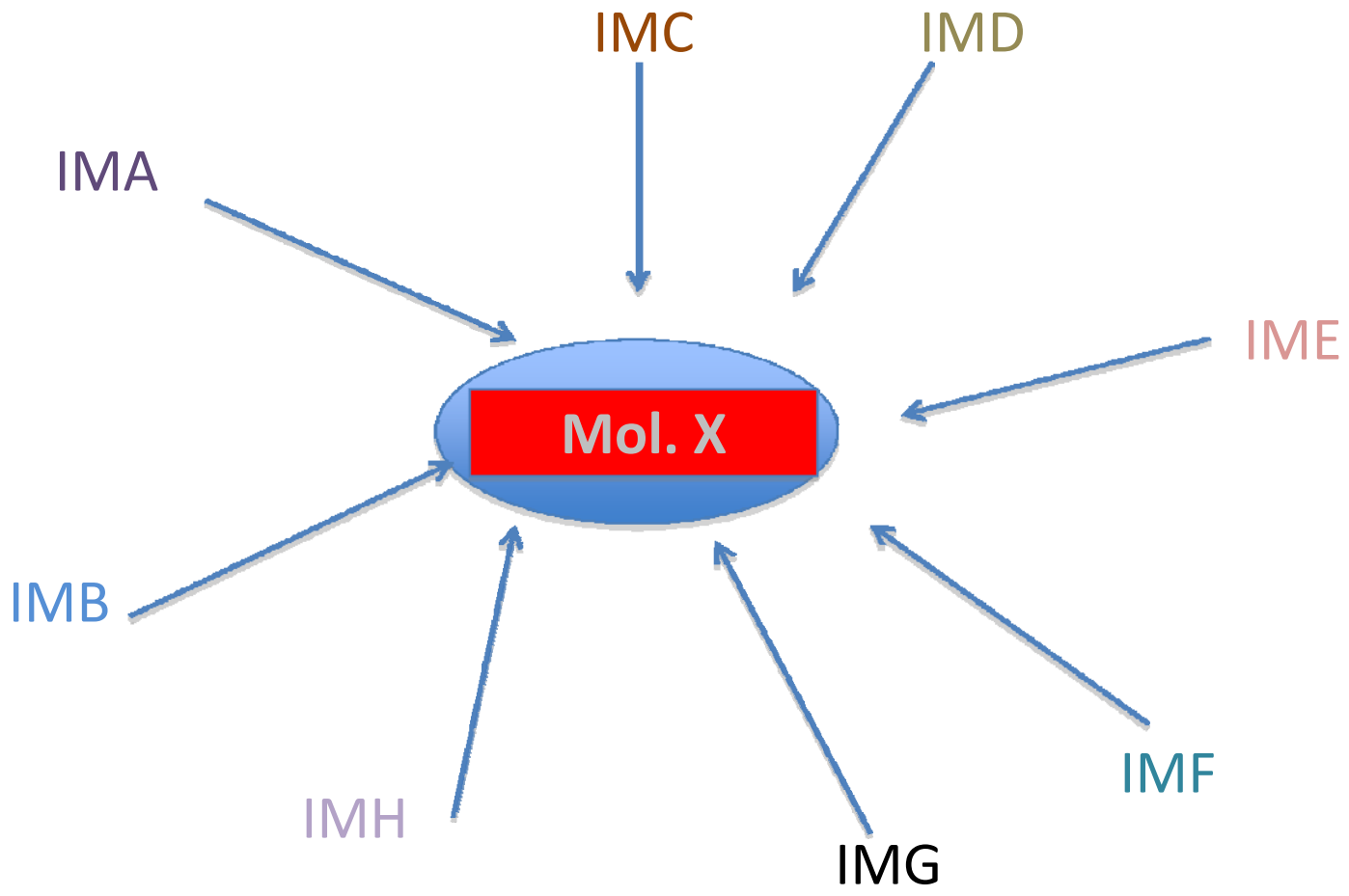
- (also cases of Gillan Barre, meningitis, etc)

Case: Raptiva

Comment:

- (Developmental)Immunossupression is Obviously Expected
- Impact of use during Pregnancy?
- Would (have) preclude(d) pediatric use?

EMA Scientific Advice: Case 1



SA: Case 1

SA: Case 1

- **Molecule X:**
  - Pathway Inhibitor affecting the cascade of multiple immune mediators.
  - Immunossupressant
  - Developed for multiple diseases including
    - Psoriasis
    - Reumathoid arthritis
    - ulcerative colitis
    - Chron's disease

Case 1: Nonclinical

- **Mol X Toxicity studied in rats and NHP**
  - primary effects: decreases in WBC, lymphocytes, and T-lymphocyte subsets
  - secondary effects: lymphoma, lymphoid hyperplasia, bacterial, and/or viral infection related to immunossuppression
  - embryofetal toxicity (teratogen)
  - Pre-post natal study ongoing

Case 1: Reprotoxicity

- **General Statement in Dossier***:*

Due to the fertility, pregnancy and embryo-foetal developmental effects (rabbits & rodents, similar to other immunossupressants), precautions to prevent pregnancy for women of childbearing potential would be necessary.

- *Comment: what about treatment of paediatric population? DIT study needed? Nice or Need to know?? To be Discussed with Sponsor*

PIPs Cases

- Most DIT concerns are raised in relation to immunomodulators / Mabs with immunomodulatory properties

- Frequently questioning:
  - -potential effect in the development of the Immune system
  - Potential effects on immune responses of developing systems (PD in juveniles?)
  - Reversibility of expected effect (if related to MOA)
  - How to extrapolate generated results
  - Which impact results will have on pediatric use

PIPs: Some Examples (1)

- 1- Anti TNF alpha (psoriasis, RA, etc. etc.)
- Embryo-fetal development study (segment II) in NHP (fetal exposure confirmed)
- no signs of fetotoxicity or teratogenicity

- **No JAS required (immune effects expectable and predictable)**

PIPs: Some Examples (2)

- Mab targeting B cells
- Immunotox included in repeated dose study
  - IgG/IgM responses preserved.

- PPND in NHP ongoing with immune system examination

- Applicant planned JAS in case of findings in PPND study

NcWG/PDCO:

Study not needed in case findings of PPND are those expected only.

PIPs: Some Examples (3)

- Anti IL-x drug
- Intended for juvenile arthritis, from age of 4.
- Ongoing Reprotox in NHP.

NcWG/PDCO:

Study need will depend on the findings of PPND study.

Some Regulator's Thoughts on DIT

- Discussion/Concern mostly driven towards Biologics.
  - Mostly immunomodulators
  - But also other proteins may be a challenge (eg autoimmunity?)

- Small molecules are studied for immunotoxicity signs in repeated dose studies.
  - In case of concerns DIT could be included in the Reprotox study. Case-based!

Some Regulator's Thoughts on DIT

- **Factors of Need**
  - Findings in repeated dose studies
  - Mode of Action
  - Therapeutic Indication (use in pregnancy)
  - Target pediatric age
- **Factors to Decide after Decision for Request**
  - Species/model selection
  - Study design
  - Interpretation of results
  - Impact of findings on drug use

Some Regulator's Thoughts on DIT

- In JAs: Mainly needed when findings are unrelated to MOA? (exclude most Mabs)
- In F1 generation: mainly needed to address reversibility?
- Should preferably integrate in PPND studies (if need identified).
- Need to adjust guidance?
- Species selection:
  - Can/shall NHP be avoided?
  - homologus molecules are of value here?

Some Challenges

- DIT evaluation might start with WOE approach (eg PD, literature data, knowledge on class effects, mechanistic knowledge, … …).

- Should be addressed when eg
  - Signals emerge from eg general toxicity studies
  - Progeny exposure is expected
  - Pediatric use is anticipated

- If needed, DIT could be included in PPND studies

- Would be desirable not to increase NHP use

The Biggest Challenge

- **Interpretation of Results:**
  - Adverse effects in healthy animals extrapolable into the diseased conditions?
  - Specially for immmunomodulators?
  - Eg Abatacept case: RA is autoimmune condition ….possible to differentiate from drug-triggered autoimmunity?
  - EF tox: compare effect of (inflammatory) maternal disease vs treatment.
  - Relevance of findings?
    - in utero vs extauterine exposure.

LEARNING…! ! !

THANK YOU!!

Developmental Immunotoxicity

- Study in growing individuals of (potential)compound effects potentially affecting
  - The Immune system
  - The immune function

  When administered during pregnancy or post-partum.