Immune-response and adverse reactions:

PRCA case example

Nicole Casadevall
Recombinant human erythropoietin (rhUEPO)

- 1985: EPO gene cloned
- 1986: first clinical trials in CKD
- 1988: rhEPO is licensed for hemodialysed chronic kidney disease (CKD) patients
- Further licenses
  - CKD patients non dialysed
  - peri-surgery – autotransfusion programs
  - anaemia of prematurity
  - patients with anaemia of cancer
  - patients with lymphoproliferative syndromes
PRCA with antibodies to EPO

1988 → 1998

- Only three cases of allo-antibodies published
  - Bergrem H et al 1993
  - Peces R et al 1996
  - Prabhakar SS et al 1997
Anemia refractory to EPO

PRCA (diagnosis)

EPO alfa SC (Eprex®)

EPO alfa IV (Eprex®)

EPO beta SC (NeoRecormon®)

EPO beta IV (NeoRecormon®)

Darbepoetin alfa (Aranesp®)
Epo antibody mediated PRCA
Diagnosis

• Unexplained loss of effect (LOE)
• Anaemia (Hb decreases by about 0.1 g/dl/day)
• Low reticulocyte count (< 10 000/µl)
• Platelets. White blood cells : normal

• Bone marrow (strongly recommended)
  – Normal cellularity
  – Erythroblasts very rare (< 5 %)
• Positive Epo antibody test
PRCA and epoetin treatment

• Virtually all cases observed in renal patients (2 cases in MDS patients)
• No cases in cancer patients
• High correlation with SC exposure to Eprex®
• No cases with exclusive IV exposure
• Median time from first exposure to anaemia: 11 months (range: 3–90 months)
Increase in PRCA coincides with changes in EPREX® formulation in 1998

• Human serum albumin (HSA) removed to comply with new European regulations

• Replaced with Polysorbate 80 (Tween 80)
EPO alfa (Eprex) outside USA

• Epoetin α formulation in US still contains HSA

- No increase in EPO-associated PRCA in USA
Change in formulation

• Clinical pharmacokinetic/pharmacodynamic study in healthy volunteers

• Physico-chemical characterization studies

• Stability – purity studies

(Comparison new/old formulation)

• No clinical studies required
Increase in PRCA Mechanisms?

• New formulation may be
  - less stable?
  - more immunogenic?

• Several hypotheses
  (micelles? leachates?)
Increase in PRCA Mechanisms ? Multifactorial ++++

- New formulation

- Cold chain respect (handling – storage)

- Route of administration (SC/IV)

- Patient (CKD – Cancer)

- Concomitant medications

- Length of treatment

- Other factors ?
Chronology of EPREX Ab-mediated PRCA

(All Spontaneous CKD Reports Received by 30 June 2007)

Number of antibody-positive PRCA cases

Year in which loss of efficacy occurred

- Polysorbate 80 syringes
- Coated Stoppers
- Contraindication of s.c. use (EU, CH)
- PRCA awareness and publications

Year
- 1989
- 90
- 91
- 92
- 93
- 94
- 95
- 96
- 97
- 98
- 99
- 00
- 01
- 02
- 03
- 04
- 05
- 06
- 07Q2

Number of cases
- 1989: 1
- 1990: 1
- 1991: 1
- 1992: 1
- 1993: 6
- 1994: 8
- 1995: 30
- 1996: 66
- 1997: 73
- 1998: 66
- 1999: 73
- 2000: 18
- 2001: 6
- 2002: 2
- 2003: 9
- 2004: 0
Reinstatement of EPREX sc in CKD

- Exclusive use of coated stopper seringes since March 2004: 3 cases in the world (excluding Thailand) with the new formulation
- Strict control of handling (cold chain)
- New FluroTec coated stopper product for sc use approved in:
  - All major markets
    - European Union
    - Switzerland
    - Australia
    - Canada
  - Others (…Thailand)
Antibody-positive PRCA cases

- ≥ 237 cases in CKD patients treated with ESA
  - 189 treated with HSA-free epoetin alfa (Eprex®, Erypo®) only
  - 10 treated with epoetin alfa (Epogen®, Procrit®) only
  - 12 treated with epoetin beta (Neorecormon®) only
  - 2 treated with HSA-free darbepoetin alfa (Aranesp®) only
  - ≥ 24 mixed cases

- 4 cases in non-CKD patients treated with ESA
  - 2 MDS patient treated
  - 2 patients with hepatitis C (+ Interferon and Ribaverin)

- (2 cases in CKD patients treated with biosimilars)
Incidence of EPO Ab-mediated PRCA

• Only reported using erythropoiesis stimulating agents (ESA) subcutaneous

• Very rare

• ARANESP® and Epogen < 1 case/ 100,000 PY
• NEORECORMON 1-2 cases/100,000 PY
• EPREX - in the world except Thailand 3/120,000 PY
  - in Thailand 9/6,500 PY
PRCA in Thailand

- Epo Ab-mediated PRCA is more common than in other countries

- Most cases reported with Eprex (9 cases) but also with:
  - Recormon®
  - Hemax® (local biosimilar)
PRCA in Thailand

• Storage and cold chain not guaranteed at out-of-hospital pharmacies

• No tracability – substitution is frequent

• 7 marketed biosimilars

• Thai FDA announced that products are illegally imported

• Counterfeit products

A Thai « loss of effect » registry is set-up run by hematology, nephrology and hospital pharmacy associations
Antibody-mediated PRCA - Summary

• Development of antibodies cannot be anticipated (very rare cutaneous reactions/hypereosinophilia)

• When antibodies are detected « it is too late »

• Diagnosis of ESA-induced Ab-mediated PRCA requires a reliable test for detection of anti-EPO Ab (sensitive – specific – reproducible – standardized)
Antibody mediated PRCA - Summary

• Is usually very rare
  - Background incidence 1-3/100,000 PY

• Has been reported with all ESAs – injected subcutaneously

• Immunogenicity cannot be detected in pre-approval clinical studies (number of patients)

• Only robust post-marketing risk management programs will be able to capture these very rare events
Ab mediated PRCA - Summary

• Minor modifications of biological products can alter their characteristics and immunogenicity
• It cannot be assumed that all products (biosimilars) have the same immunogenicity profile
• Improper handling and storage can alter the safety profile of ESA
• Substitution will be unavoidable… but should be as infrequent as possible
• Traceability of all ESA given to a patient is essential
• If the same INN is given to different biosimilars, traceability will be almost impossible
• Ideally… serum sample should be stored before any switch is made … but this seems to be very difficult in clinical practice
• IV route of administration should be promoted in hemodialysis patients, for safety reasons