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GaBI Scientific Meetings

ROUNDTABLE ON BIOSIMILARS
with participation by European Regulators and Medical Societies

12 January 2016, Sheraton Brussels Airport Hotel, Belgium

Unwanted immunogenicity of biothera-peutic products including biosimilars

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Deputy Editor-in-Chief, GaBI Journal
12 January 2016

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Unwanted Immunogenicity of Biotherapeutic Products including Biosimilars

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Unwanted Immunogenicity

- Biological products (including biosimilars) can induce antibodies with different characteristics:
  - Non-neutralizing (binding) antibodies against active (and/or inactive) product-related substance(s).
  - Binding antibodies against contaminants.
  - Neutralising antibodies.
  - Mixtures of the above.
- But antibodies are not necessarily induced by biologicals/biosimilars. Incidence varies.

Potential Clinical Consequences of immunogenicity

- Can range from benign, non-significant to serious life-threatening depending on the therapeutic
- Consequences on efficacy- reduction of the clinical response to the biotherapeutic
- Consequences on safety- safety issues can occur even when there is no loss of efficacy

Acute consequences

- Infusion reactions, anaphylactic reactions

Non-acute consequences

- Delayed-type hypersensitivity/immune complexes
- Cross-reactivity with an endogenous counterpart

Factors Influencing Unwanted Immunogenicity

Product and Patient related

- Molecular structure, novel epitopes, glycosylation, degradation, oxidation, deamidation
- Product impurities
- Formulation
- Aggregation
- Protein – biological properties e.g., immunostimulant
- Dose, route, frequency of administration and duration of therapy
- Immune status, age, genetic profile, disease, treatment
- Previous exposure

Antibodies and Adverse Effects

The New England Journal of Medicine

VOLUME 346 FEBRUARY 14, 2002 NUMBER 7

PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

NICOLE CASADEVALL, M.D., JOELLE NATAF, M.D., BEATRICE VIRON, M.D., AMIR KOLTA, M.D., JEAN-JACQUES KILADJIAN, M.D., PHILIPPE MARTIN-DUPONT, M.D., PATRICK MICHAUD, M.D., THOMAS PAPO, M.D., VALÉRIE UGO, M.D., IRÈNE TEYSSANDIER, B.S., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.

Eprex: Formulation change (1999)
Cause: Leachates from uncoated stoppers (adjuvant).
Formulation/Containers: risk factors

PRCA cases in Thailand, Korea - many marketed products

blood

2001 98: 3241-3248
doi:10.1182/blood.V98.12.3241

Thrombocytopenia caused by the development of antibodies to thrombopoietin

Junzhi Li, Chun Yang, Yuping Xia, Amy Bertino, John Glaspy, Michael Roberts and David J. Kuter

Cross-reactivity with endogenous protein

- MAb against EGFR – colorectal cancer, squamous cell carcinoma of head and neck
- 25/76 patients experienced hypersensitivity
- 17 had pre-existing IgE antibodies against gal-α-1, 3 gal present on Mab (expressed in murine myeloma cells)
- Cases clustered in different US states; IgE antibodies potentially due to tick bites etc

N Engl J Med. 2008 March 13; 358(11): 1109–1117.

Cetuximab-Induced Anaphylaxis and IgE Specific for Galactose-α-1,3-Galactose

Christine H. Chung, M.D., Beloo Mirakhur, M.D., Ph.D., Emily Chan, M.D., Ph.D., Quynh-Thu

Clinical Impact

- Efficacy – impaired clinical response
- Safety – Infusion reactions, hypersensitivity reactions, serum sickness
  – Cross-reactivity with an endogenous counterpart

Actas Dermosifiliogr. 2009;100:103-12

CONSENSUS STATEMENT

Reactions to Infliximab Infusions in Dermatologic Patients: Consensus Statement and Treatment Protocol

L. Puig,[a] E. Sáez,[b] M.J. Lozano,[b] X. Bordas,[c] J.M. Carrascos,[a,d] F. Gallardo,[e] J. Luelmo,[f] M. Sánchez-Regaña,[g] M. Alsina,[h] and V. García-Patos[i] for the Spanish Academy of Dermatology and Venereology Psoriasis Working Group

with the administration of infliximab is the possibility of infusion reactions, which may be immediate or delayed; these reactions are related to the immunogenicity of this monoclonal antibody, leading to the production of anti-infliximab antibodies. Infusion reactions to infliximab are not usually anaphylactic (ie, they are not mediated by immunoglobulin E), and re-exposure of the patient using specific protocols to

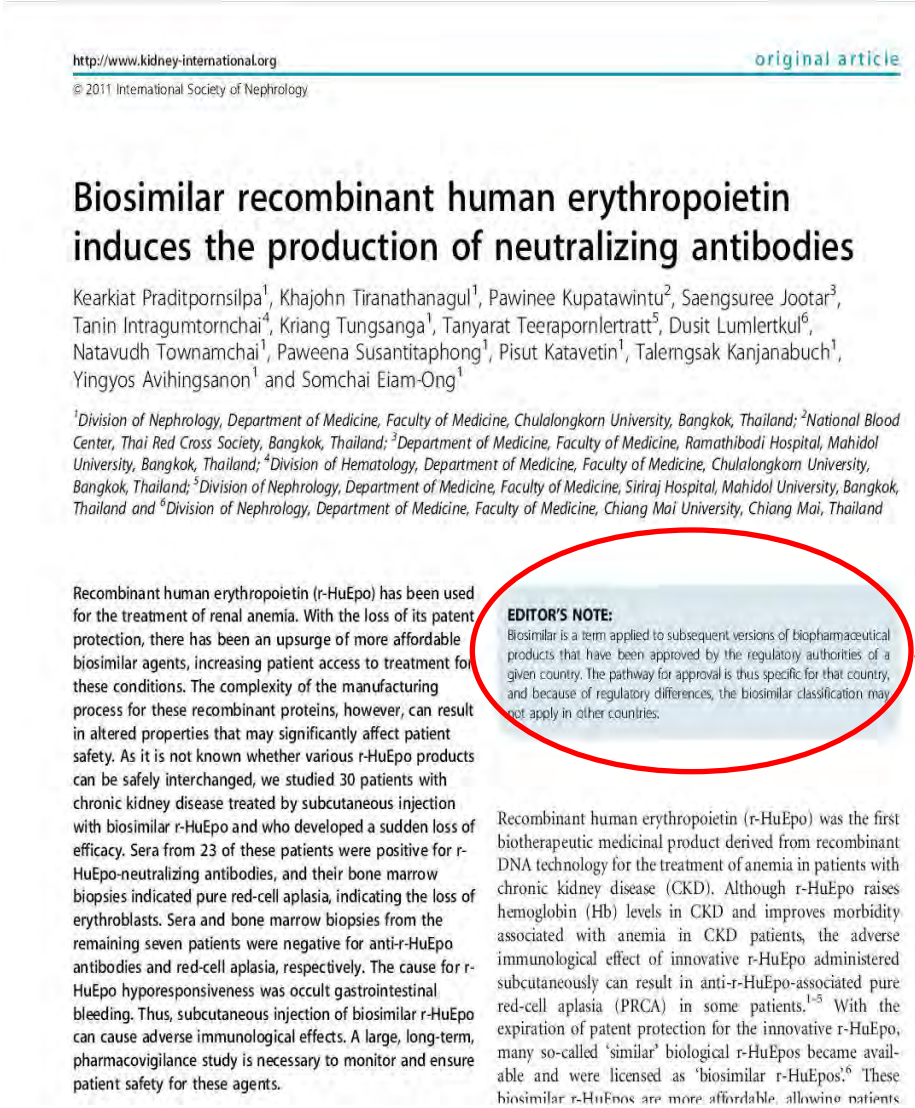
Neurology. 2013 Feb 6. [Epub ahead of print]

Fatal Neuroinflammation in a Case of Multiple Sclerosis with Anti-Natalizumab Antibodies.

Svenningsson A, Dring AM, Fogdell-Hahn A, Jones I, Engdahl E, Lundkvist M, Brännström T, Gilthorpe JD.

"significant neurological abnormalities … after… six infusions of natalizumab, …. extremely high titers of antibodies against the drug."
" death..from 'rebound neuroinflammation as a result of the development of natalizumab anti-drug antibodies."

‘Biosimilar’ EPO is Immunogenic?



http://www.kidney-international.org original article

Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies

Kearkiat Praditpornsilpa[1], Khajohn Tiranathanagul[1], Pawinee Kupatawintu[2], Saengsuree Jootar[3], Tanin Intragumtornchai[4], Kriang Tungsanga[1], Tanyarat Teerapornlertratt[5], Dusit Lumlertkul[6], Natavudh Townamchai[1], Paweena Susantitaphong[1], Pisut Katavetin[1], Talerngsak Kanjanabuch[1], Yingyos Avihingsanon[1] and Somchai Eiam-Ong[1]

[1]Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [2]National Blood Center, Thai Red Cross Society, Bangkok, Thailand; [3]Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [4]Division of Hematology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [5]Division of Nephrology, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand and [6]Division of Nephrology, Department of Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Recombinant human erythropoietin (r-HuEpo) has been used for the treatment of renal anemia. With the loss of its patent protection, there has been an upsurge of more affordable biosimilar agents, increasing patient access to treatment for these conditions. The complexity of the manufacturing process for these recombinant proteins, however, can result in altered properties that may significantly affect patient safety. As it is not known whether various r-HuEpo products can be safely interchanged, we studied 30 patients with chronic kidney disease treated by subcutaneous injection with biosimilar r-HuEpo and who developed a sudden loss of efficacy. Sera from 23 of these patients were positive for r-HuEpo-neutralizing antibodies, and their bone marrow biopsies indicated pure red-cell aplasia, indicating the loss of erythroblasts. Sera and bone marrow biopsies from the remaining seven patients were negative for anti-r-HuEpo antibodies and red-cell aplasia, respectively. The cause for r-HuEpo hyporesponsiveness was occult gastrointestinal bleeding. Thus, subcutaneous injection of biosimilar r-HuEpo can cause adverse immunological effects. A large, long-term, pharmacovigilance study is necessary to monitor and ensure patient safety for these agents.

EDITOR'S NOTE:
Biosimilar is a term applied to subsequent versions of biopharmaceutical products that have been approved by the regulatory authorities of a given country. The pathway for approval is thus specific for that country, and because of regulatory differences, the biosimilar classification may not apply in other countries.

Recombinant human erythropoietin (r-HuEpo) was the first biotherapeutic medicinal product derived from recombinant DNA technology for the treatment of anemia in patients with chronic kidney disease (CKD). Although r-HuEpo raises hemoglobin (Hb) levels in CKD and improves morbidity associated with anemia in CKD patients, the adverse immunological effect of innovative r-HuEpo administered subcutaneously can result in anti-r-HuEpo-associated pure red-cell aplasia (PRCA) in some patients.[1–5] With the expiration of patent protection for the innovative r-HuEpo, many so-called ‘similar’ biological r-HuEpos became available and were licensed as ‘biosimilar r-HuEpos’.[6] These biosimilar r-HuEpos are more affordable, allowing patients

Under the generic drug paradigm of the Thai Food and Drug Administration, 14 biosimilar r-HuEpos were licensed by 1 January 2009. These products came from various countries such as Argentina, China, South Korea, and India.

The number of cases using ‘biosimilar’ r-HuEpos have increased enormously because of their more affordable prices. With their usage, adverse effects of the less than identical therapeutic agents have started to increase.

Many clinicians in Thailand were starting to see an increase in PRCA cases which raised an important issue whether the immunogenicity of biosimilar therapeutic agents were indeed equivalent to the innovative r-HuEpo.

Misleading definition

Worldwide consensus - A biosimilar is a biotherapeutic accepted by a regulatory pathway which requires biological and clinical comparison with the original licensed product. The ‘biosimilars’ described in this paper are NOT real biosimilars.

Unwanted Immunogenicity- The Most Challenging Issues

- It is impossible to predict
  - the incidence of unwanted immunogenicity
  - the characteristics of the immune response
  - the clinical consequences & significance of such immunogenicity
- THE ABOVE NEED TO BE ASSESSED IN APPROPRIATE STUDIES
- These immunogenicity studies are normally carried out as part of clinical trials.

Unwanted Immunogenicity

Current Position

Testing for unwanted immunogenicity is integral to product development (clinical & post-marketing phase) for ensuring:

- The clinical safety of a biotherapeutic
- Product Comparability
- When a Biosimilar product is developed

European Medicines Agency

London, 13 December 2007
Doc. Ref. EMEA/CHMP/BMWP/14327/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON IMMUNOGENICITY ASSESSMENT OF BIOTECHNOLOGY-DERIVED THERAPEUTIC PROTEINS

DRAFT AGREED BY BMWP	July 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	January 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	July 2007
AGREED BY BMWP	October 2007
ADOPTION BY CHMP	December 2007
DATE FOR COMING INTO EFFECT	April 2008

KEYWORDS	*Immunogenicity, unwanted immune response, biotechnology derived proteins, immunogenicity risk factors, assays, clinical efficacy and safety, risk management*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 May 2012
EMA/CHMP/BMWP/86289/2010
Committee for Medicinal Products for Human Use (CHMP)

Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use.

Draft agreed by Similar Biological Medicinal Products Working Party	October 2010
Adoption by CHMP for release for consultation	November 2010
End of consultation (deadline for comments)	May 2011
Final agreed by BMWP	March 2012
Adoption by CHMP	24 May 2012
Date for coming into effect	1 December 2012

Disclaimer: This guideline is intended as an addendum to Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins EMEA/CHMP/BMWP/14327/2006 and should be read in conjunction.

Keywords	**Immunogenicity, monoclonal antibodies, similar biological medicinal products, clinical use, assay strategy.**

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Biosimilars: Comparability Concept

Comparability studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product authorised in the Community.

Comparative Immunogenicity for Biosimilar Development

- Compares immunogenicity of different products ;

  Studies need to be designed to demonstrate whether the immunogenicity of the products is the same or significantly different.
- This will affect the design of the studies & their interpretation.
- For this, a homogeneous and clinically relevant patient population should be selected. Head-to-Head studies needed. Same assays & sampling strategy should be used.
- The consequences of immunogenicity also must be compared.
- Post-approval assessment may be necessary, usually as part of pharmacovigilance surveillance.

Antibody Frequency for Biosimilar (presubmission studies)

Biosimilar	Ab frequency	Reference	Ab frequency
Omnitrope (SC)	0/51 (0.0%)	Genotropin	1/44 (2.3%)
Valtropin (SC)	3/98 (3.4%)	Humatrope	1/49 (2.0%)
Binocrit (IV)	2/314 (0.6%)	Erypo	3/164 (1.8%)
Silapo (IV) Silapo (SC)	0/305 (0.0%) 0/323 (0.0%)	Erypo Erypo	0/304 (0.0%) 0/230 (0.0%)
Ratiograstim (SC)	7/356 (2.0%)	Neupogen	2/134 (1.5%)
Zarzio (IV / SC) (Phase 1, crossover)	0%	Neupogen	0%
Nivestim	3/183 (1.6%)	Neupogen	0/95 (0.0%)
Bemfola	0/249 (0%)	Gonal-f	0/123 (0%)
Insulin Marvel §	T1DM: 25/114 (21.9%) T2DM: 14/131 (10.7%)	Humulin	T1DM: 16/114 (14.0%) T2DM: 17/136 (12.5%)
Remsima - AS - RA	37.5% 55.6%	Remicade	36.1% 54.3%

Data from EPARs at *www.ema.europa.eu*

§ Application withdrawn.

Table courtesy of Martina Weise

Antibodies and Adverse Effects - EPO

Binocrit approved - 2007
Following rigorous physico-chemical, biological characterisation & clinical trial data
Brockmeyer & Seidl (2009) Biologicals

Safety Study for Binocrit (Biosimilar EPO) Suspended
– No increased immunogenicity from IV use in patients with renal anaemia or SC use in cancer patients (both licensed).
– Postmarketing SC trial in previously untreated renal anaemia patients: two cases of neutralising Ab development. Cause linked to syringe plungers?

Problems in Thailand:

>60 PRCA cases identified in Thailand. 16 EPO (or more) products marketed. Link to product(s) ?

Biosimilars as Biologicals

- As is clear from the EMA definition, Biosimilars are Biologicals. They differ from innovator Biologicals in the regulatory process used for their approval.
- As Biosimilars are ‘scientifically’ Biologicals they should be regarded as such when immunogenicity is being considered.
- There is no reason to treat approved Biosimilars any differently from all Biologicals (including innovator products) from the immunogenicity perspective.

Unwanted Immunogenicity; what types of Products are affected?

- Unwanted immunogenicity is a potential problem for ALL biologicals.
- The clinical implications of unwanted immunogenicity are also potential problems for ALL biologicals.
- This applies to innovator biologicals, biosimilars and non-innovator biologicals.
- It is NOT a specific problem for biosimilars.
- So far, the incidence of unwanted immunogenicity for innovator products and biosimilars is very similar.
- There may be increased immunogenicity problems for some non-innovator biologicals (as used in developing countries), but these products are NOT biosimilars.

Conclusions

- Immunogenicity issues occur all along the life cycle of a product and particularly when :
  - a new therapeutic protein is developed and used for various clinical indications
  - a change is introduced e.g. process, formulation, storage conditions etc
  - a biosimilar product is proposed
- Assessment requires
  - an optimal antibody testing strategy
  - validated methodologies and reference standards

Acknowledgements

Meenu Wadhwa

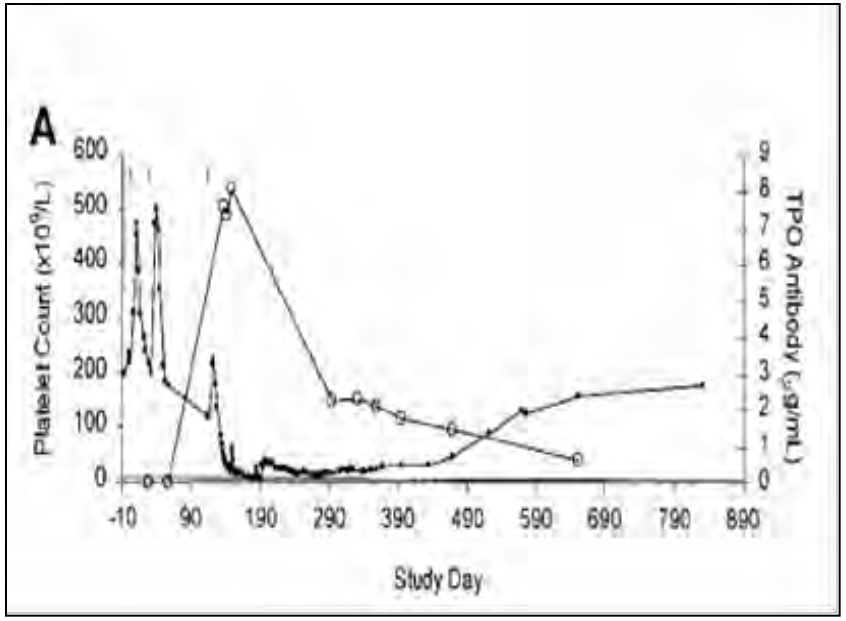
Colleagues of the BMWP

Antibodies and Adverse Effects; Classic Examples-

MGDF administered to patients caused thrombocytopenia.

-Cancer patients 4/650;

-healthy patients 13/325



Product development terminated

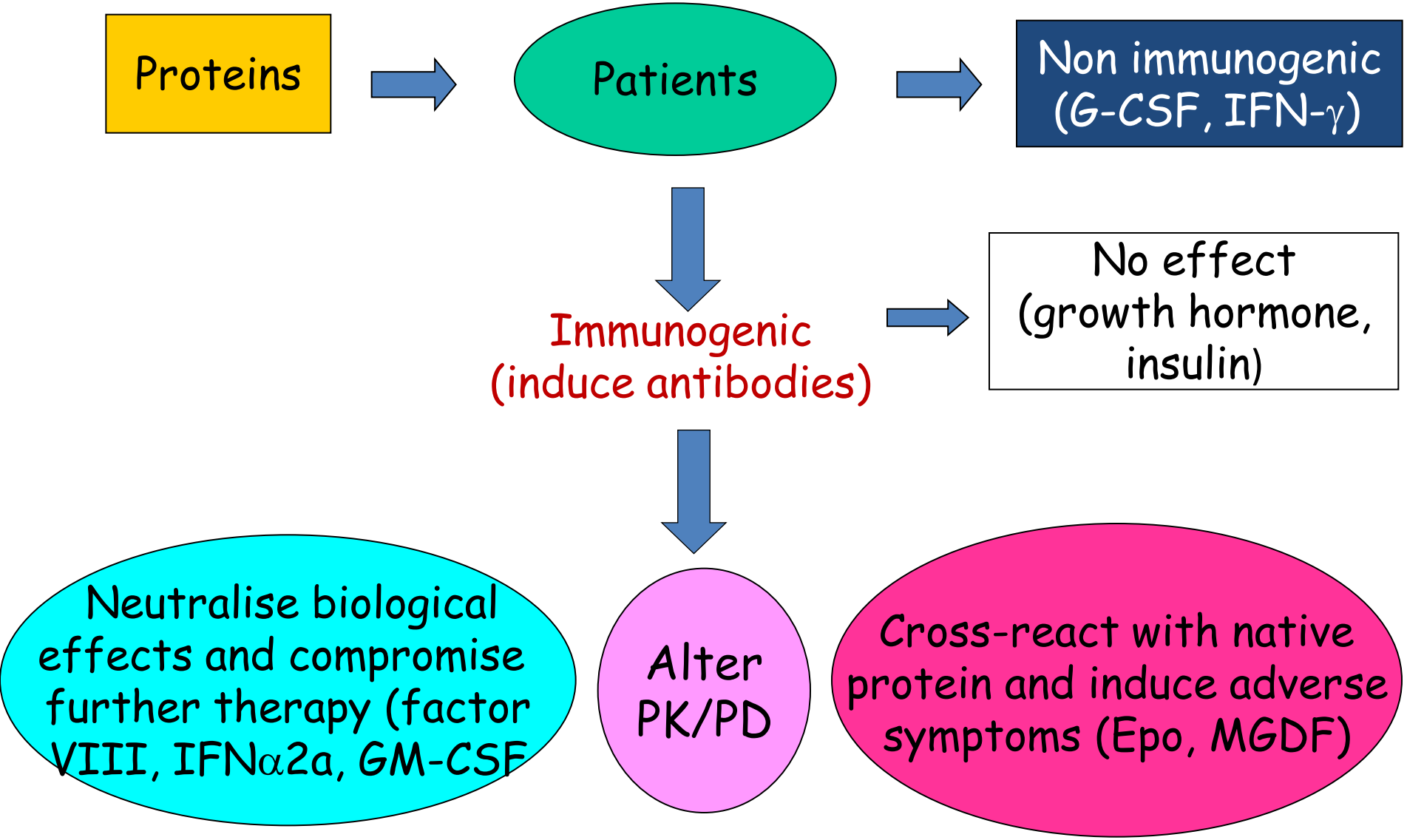
Pure red-cell aplasia (PRCA) and anti-EPO antibodies in patients treated with EPO (EPREX)

- Pre 1998 – 2/3 cases
- 2002 - 13 cases in chronic renal failure patients, rapid development of severe transfusion dependence within months of therapy, resistant to other EPO products
- 1998 to June'05 – 260+ cases worldwide (probably an underestimate).

Cause(s) ?

Casadevall N, et al. *N Engl J Med.* 2002;346(7):469-475.

Unwanted Immunogenicity



Product Name	Protein	Indication	% Patients with Immune Response
Intron A Roferon Pegasys PegIntron	IFN-α2a	Hepatitis C	7 25 9 1
Betaferon Avonex Rebif	IFN-β	Multiple Sclerosis	25 – 45 2 – 6 12 – 28
Eprex, Procrit Neorecormon, Aranesp	Epo	Anemia	Rare
Neupogen, Nivestim	G-CSF	Myeloregeneration, neutropenia	0-1.5 1.6
Leukine, Leucomax	GM-CSF	Myeloregeneration, immunostimulation	2 – 95
Proleukin	IL-2	Oncology	47–74
Rituximab	Anti-CD20	NHL SLE	0 65
Humira	Fully human anti-TNFα	RA	12 -28
Remicade	Chimaeric anti-TNFα	Crohn's RA	61 12

Biosimilars: Unwanted Immunogenicity

Quote from EMEA BMWP chairmen:

‘Unwanted Immunogenicity is the biggest challenge for the approval of Biosimilars’

Correlation of Antibody Induction with Reduced Clinical Efficacy

In some cases development of (neutralizing) antibodies in patients clearly can reduce the clinical response to the product.

Examples of this are Remicade (anti-TNF alpha), Tysabri (anti-alpha 4 integrin), Humira (anti-TNF alpha).

In other cases there is less clear correlation e.g. Rituximab (anti-CD20).

This makes interpretation and particularly prediction of the clinical effects of antibody development difficult, and generalizations concerning this dangerous.