GaBI Educational Workshops

3rd Colombian Educational Workshop on
REGULATORY ASSESSMENT OF BIOSIMILARS

30 April 2019, Hilton Bogotá, Colombia

Robin Thorpe, PhD, FRCPath, UK

- Former Head of Biotherapeutics Group, National Institute for Biological Standards and Control, UK

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Immunogenicity studies for assessing biosimilar products

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Immunogenicity studies for assessing biosimilar medicinal products.

Robin Thorpe PhD, FRCPath
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Biosimilars in the EU

Biosimilars are now firmly established in the EU as copy biologicals with a clear and effective regulatory route for approval, which allows marketing of safe and efficacious biosimilar products.

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

Antibodies and Adverse Effects

The New England Journal of Medicine

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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., BÉATRICE 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

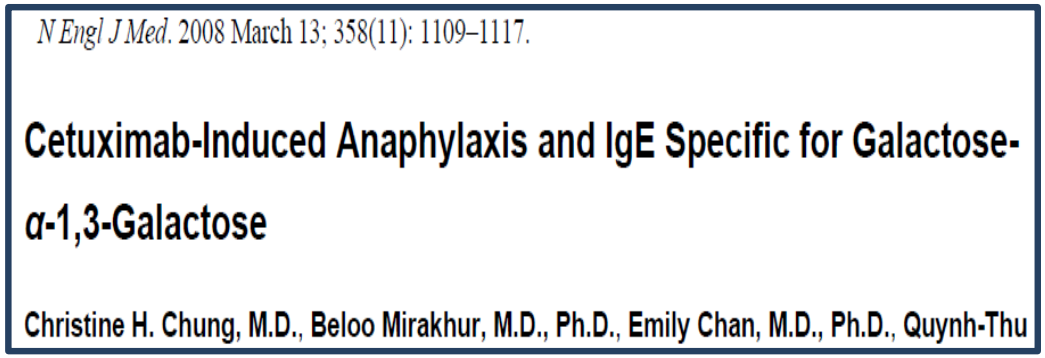
Thrombocytopenia caused by the development of antibodies to thrombopoietin

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

Product with same antigen as natural immunogen



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

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).

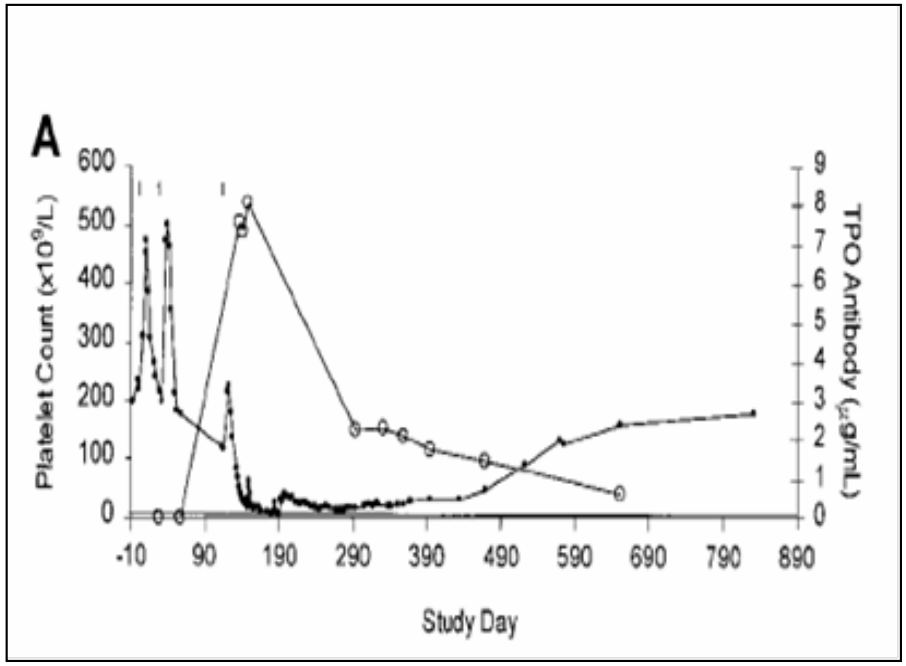
In other cases there is less clear correlation, e.g. Rituximab (anti-CD20).

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

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.

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

Complexity of Proteins

Any subtle (small) change introduced in the manufacturing process of a given product can have enormous implications for immunogenicity.

And vice-versa.

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

Immunogenicity Testing: A Tiered Approach

Screening assays - for ‘identification’ of all anti-therapeutic antibodies

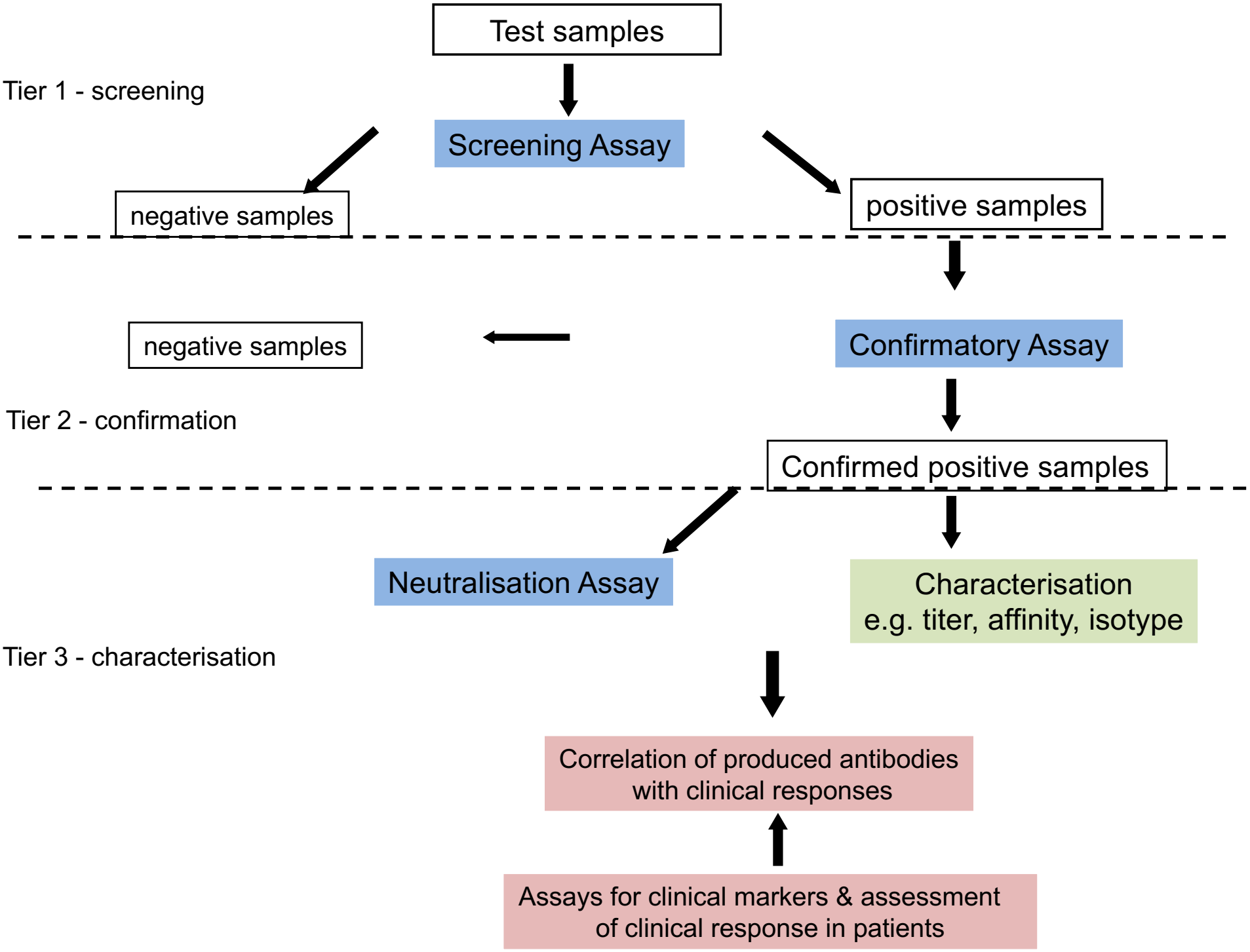
- ELISAs - direct, bridging, other formats
- Radioimmunoprecipitation assays (RIPA)
- Surface Plasmon Resonance (SPR)
- Other technologies

Confirmatory assays – for confirming antibodies

Other assays – for specificity of the antibodies

Neutralization assays – for discriminating neutralizing & non-neutralizing antibodies.

- Cell-based assay or
- Non-cell-based ligand binding assay


Test samples
Tier 1 - screening
Screening Assay
negative samples
positive samples
negative samples
Confirmatory Assay
Tier 2 - confirmation
Confirmed positive samples
Neutralisation Assay
Characterisation
e.g. titer, affinity, isotype
Tier 3 - characterisation
Correlation of produced antibodies
with clinical responses
Assays for clinical markers & assessment
of clinical response in patients

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.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 May 2017
EMEA/CHMP/BMWP/14327/2006 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Immunogenicity assessment of therapeutic proteins

Draft revision agreed by Biosimilar Medicinal Products Working Party (BMWP)	August 2015
Adopted by CHMP for release for consultation	24 September 2015
Start of public consultation	01 October 2015
End of consultation (deadline for comments)	31 January 2016
Agreed by Biosimilar Medicinal Products Working Party (BMWP)	November 2016
Adopted by CHMP	18 May 2017
Date of coming into effect	01 December 2017

This guideline replaces 'Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins' (EMEA/CHMP/BMWP/14327/2006).

Keywords	***Immunogenicity, therapeutic proteins, anti-drug antibodies (ADA), assays, assay strategy, binding antibodies, neutralising antibodies, risk factors, safety, efficacy, pharmacokinetics, risk management, integrated summary of immunogenicity***

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.

This applies to the immunogenicity assessment.

Comparative Immunogenicity

- 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 is likely to 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.

Immunogenicity Studies: Biosimilars

The immunogenicity of the marketed product does not influence the need for comparative immunogenicity studies.

However, if the immunogenicity profiles of marketed and biosimilar products are significantly different, they can be considered DISSIMILAR

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) ?

‘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]

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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; 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

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

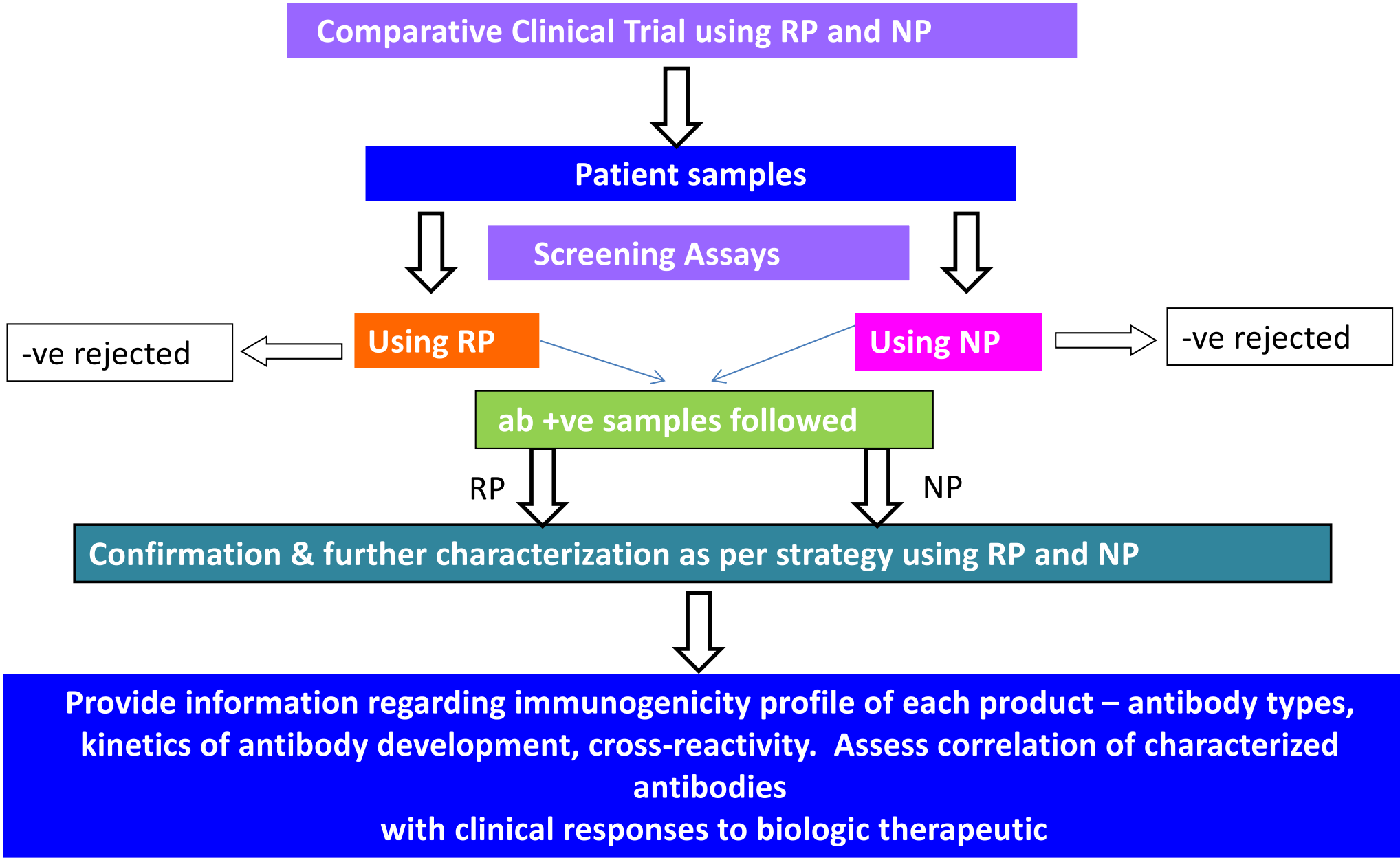
Neurology. 2013 Feb 6. [Epub ahead of print]

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."

Relative Immunogenicity



Relative Immunogenicity