Immunogenicity Guideline mAbs
A risk-based approach - rationale and decision points
Closed Workshop on biosimilar monoclonal antibodies and immunogenicity of monoclonal antibodies October 2011

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Clinical safety: Depends on the product

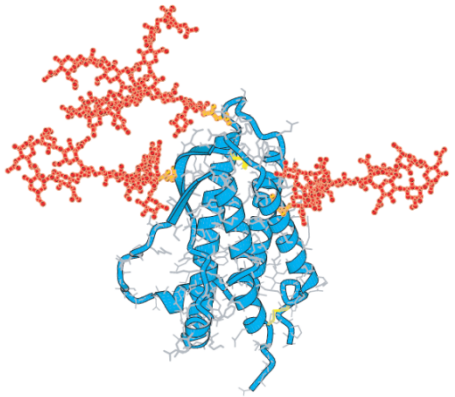
Erythropoietin: High-risk product

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., 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.



Courtesy of M.R. Wormald and R.A. Dwek, Oxford Glycobiology Institute, and P.M. Rudd, NIBRT

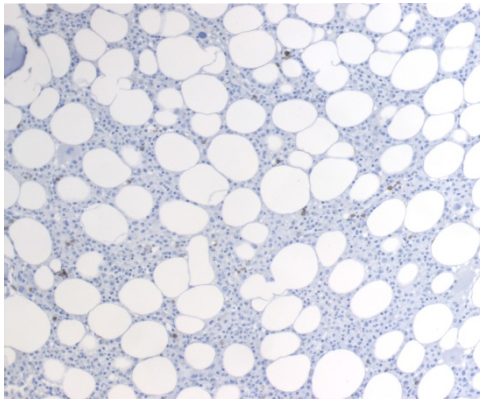
Molecular model of erythropoietin with complex N-linked glycans at sites N24, N38 and N83. The glycan-protein linkages are likely to exhibit considerable flexibility; the structure shown is just one possible conformation.

CLINICAL TRIALS AND OBSERVATIONS

Long-term outcome of individuals with pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project

Charles L. Bennett, Denis Cournoyer, Kenneth R. Carson, Jerome Rossert, Stefano Luminari, Andrew M. Evens, Francesco Locatelli, Steven M. Belknap, June M. McKoy, E. Alison Lyons, Benjamin Kim, Rishi Sharma, Stacey Costello, Edwin B. Toffelmire, George A. Wells, Hans A. Messner, Paul R. Yarnold, Steven M. Trifilio, Dennis W. Raisch, Timothy M. Kuzel, Allen Nissenson, Lay-Cheng Lim, Martin S. Tallman, and Nicole Casadevall

BLOOD, 15 NOVEMBER 2005 • VOLUME 106, NUMBER 10



Clinical safety: Depends on product

ORIGINAL RESEARCH

Managing Cetuximab Hypersensitivity-Infusion Reactions: Incidence, Risk Factors, Prevention, and Retreatment

Thomas J. George, Jr, MD, FACP, Kourtney D. LaPlant, PharmD, Edmund O. Walden, PharmD, BCOP, Arlene B. Davis, RN, MSN, AOCN, Charles E. Riggs, MD, Julia L. Close, MD, Sarah N. George, MA, and James W. Lynch, MD

The Journal of Supportive Oncology Volume 8, Number 2 ■ March/April 2010

Tumori, 96: 473-477, 2010

Successful treatment with the fully human antibody panitumumab after a severe infusion reaction with cetuximab

Wolfram Brugger

Schwarzwald-Baar Clinic, Villingen-Schwenningen, Teaching Hospital, University of Freiburg, Germany

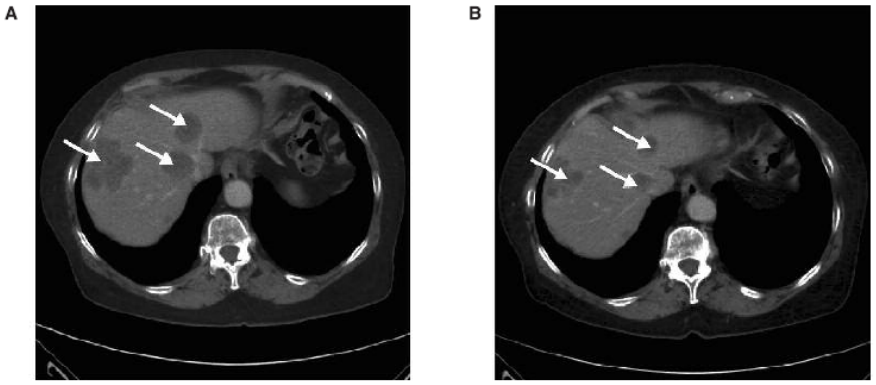


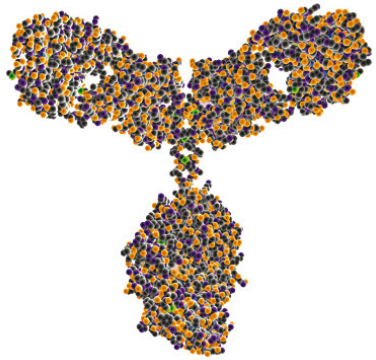
Figure 2 - Computed tomography scans of the patient's liver (A) before and (B) after 2 months of panitumumab therapy, showing response to treatment.

OBSERVATION

Allergic and Nonallergic Delayed Infusion Reactions During Natalizumab Therapy

Kerstin Hellwig, MD; Sebastian Schimrigk, MD; Malte Fischer, MD; Aiden Haghikia, MD; Thomas Müller, MD; Andrew Chan, MD; Ralf Gold, MD

Arch Neurol. 2008;65(5):656-658

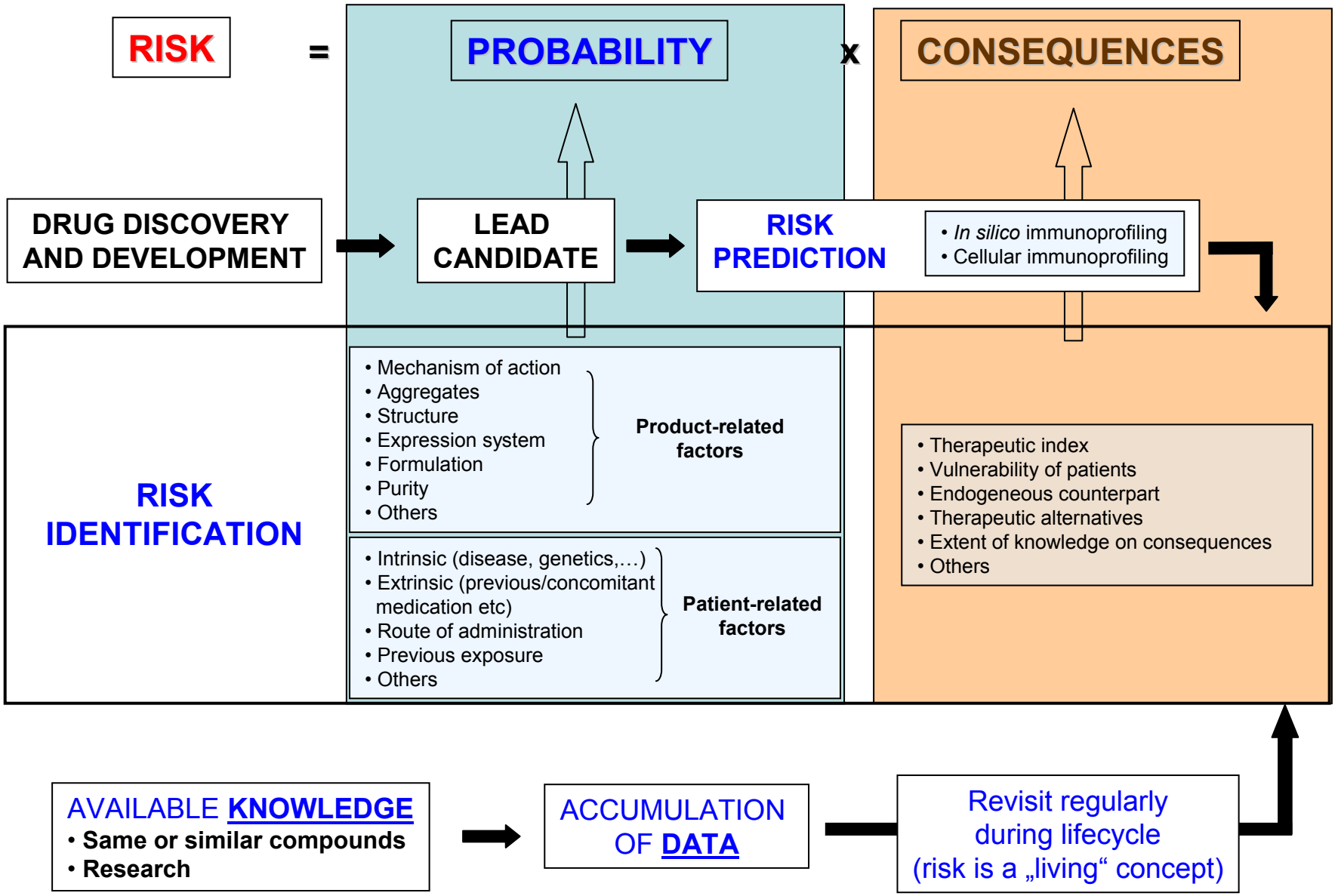


Monoclonal antibodies: Low(er) risk?

The draft CHMP guideline: Immunogenicty of mAbs

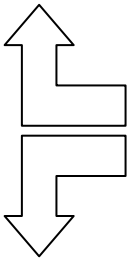
- Some specific aspects of immunogenicity are exclusively or primarily relevant for mAbs, novel mAb derivatives (eg Fab fragments, scfv, nanobodies, minibodies) or biosimilar mAbs and these are addressed in this guideline.
- Anti-antibody antibodies are a technological challenge.
- Can we define what „risk“ is and can we handle it?

What is „risk“?



Taking „risk“ to next level: Risk assessment

RISK IDENTIFICATION **(…see previous slide)**



Available **knowledge**
- same compound
- similar compounds
- **research**

accumulation of **data**

Assay finetuning
(e.g., increasing sensitivity on the cost of increased false positives)

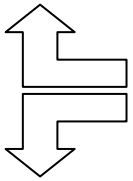
Assay design
Clinical readout(s) (safety and efficacy)
(available? Standardized? Feasibility in clinical practice?)

RISK ASSESSMENT
(= **Translation** of findings/assumptions)

Ability / Necessity…
- … to control factors?
- … to early (e.g., IgM) and reliably detect unwanted immune responses
- … to detect loss of efficacy in absence of control
- … to trace patients

Taking „risk“ to next level: Risk mitigation

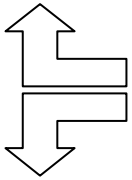
RISK IDENTIFICATION *(…see previous slide)*



Available **knowledge**
- same / similar compounds
- **research**

accumulation of **data**

RISK ASSESSMENT *(…see previous slide)*



Available **knowledge**
- same / similar compounds
- **research**

accumulation of **data**

Revisit during Lifecycle („living“ concept)

RISK MINIMISATION / MITIGATION

- standardisation / systematic approach (within development – between manufacturers)
- extent of safety database pre-approval (including frequency of sampling)
- need to control for risk factors in clinical trial?
- need to power for safety rather than efficacy?
- extent of post-marketing activities
- extent of analysis * IgM ? (early stop-of-treatment decision for high-risk compounds?)
  * IgG subclasses ?

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journal homepage: www.elsevier.com/locate/biologicals

Taking immunogenicity assessment of therapeutic proteins to the next level

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Biologicals 39(2):100-9. Epub 2011 Feb 24.