Pharmacovigilance
Special clinical pharmacological aspects

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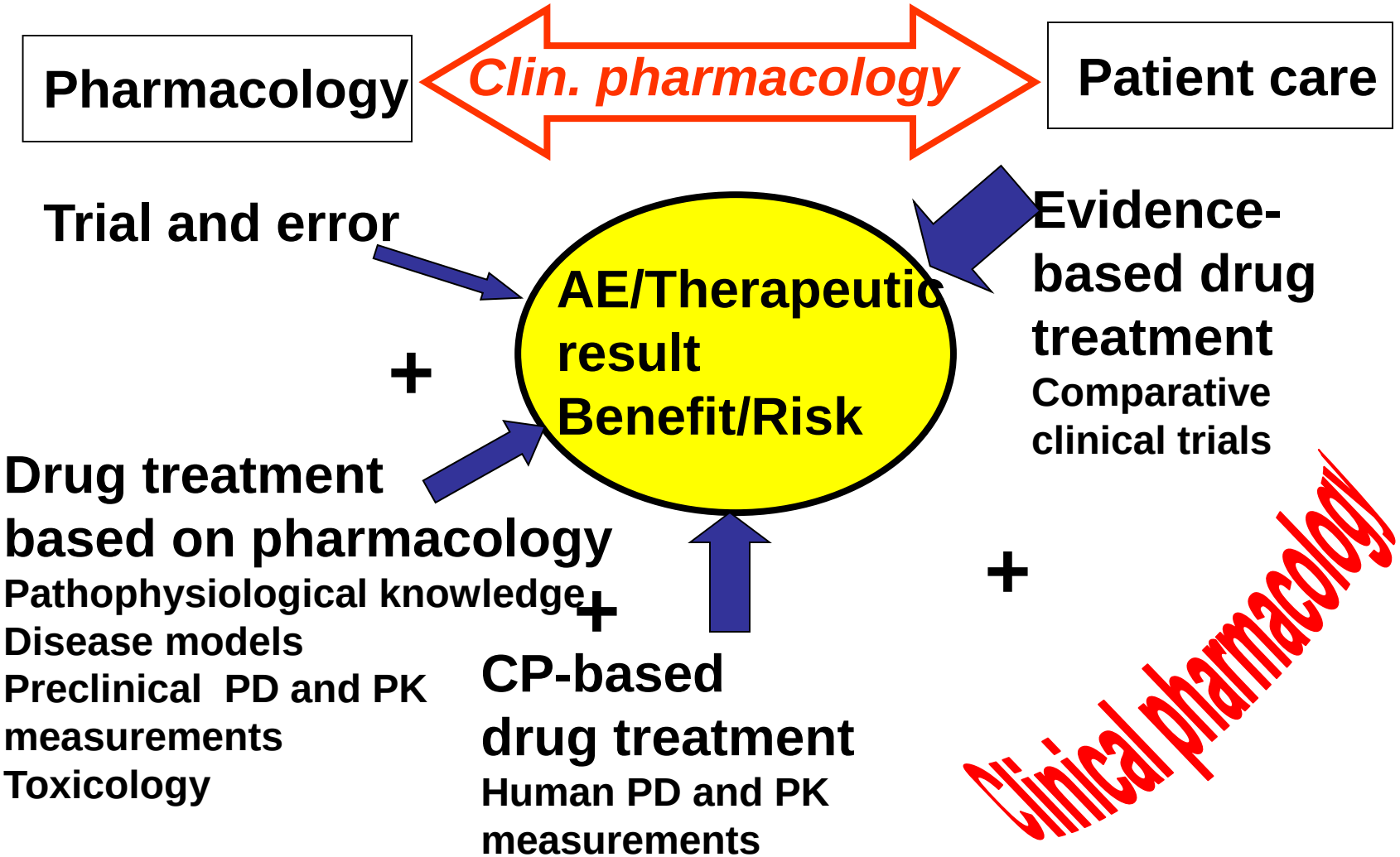
The place of clinical pharmacology (CP) in medicine



* PD=pharmacodynamics; PK=pharmacokinetics

Evaluation of a medicinal product

The life cycle of drugs

P A T E N T

Data exclusivity

New drug	Experi-mental drug	Marketed drug	*Generic biosimilar drugs*
preclinical pharmacologic toxicolologic studies	phase I phase II phase III studies	Postmarketing phase IV, prospective, randomized, comparative trials observational and controlling studies	*comparative biovailability or pharmaco-dynamic studies*

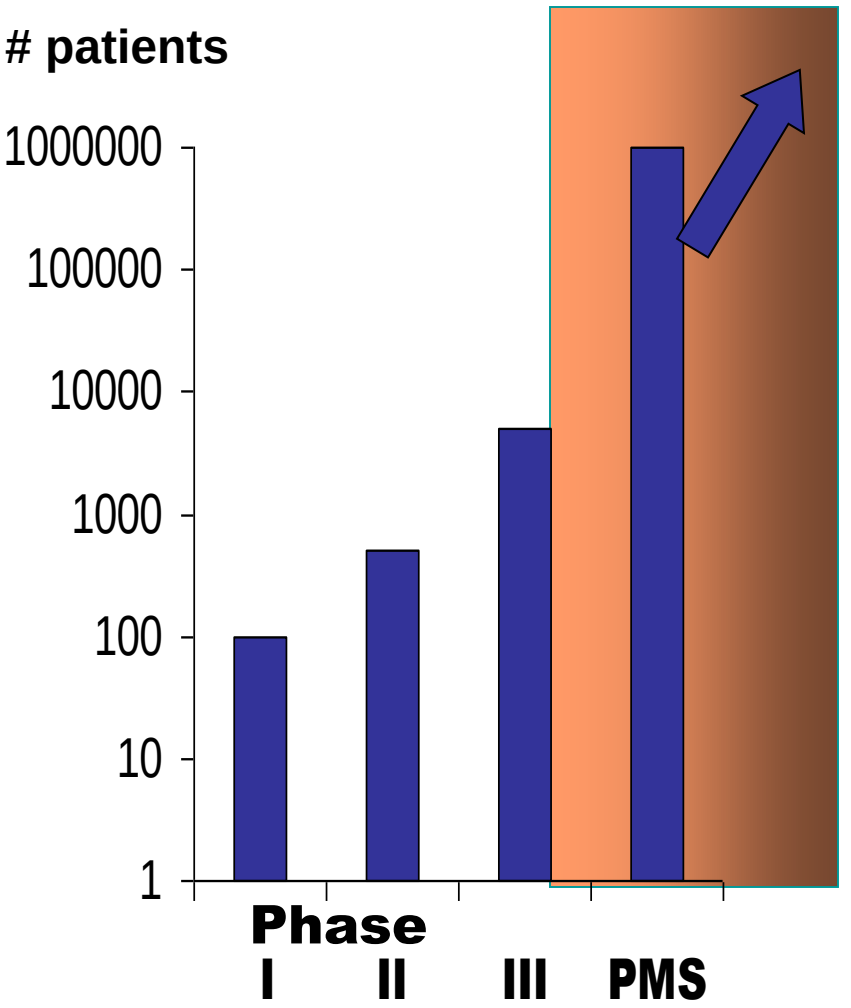
Adverse event reporting

Adverse event reporting

- ***During drug development*** *the documentation of adverse events is compulsory for assessing the risk/benefit ratio for authorisation*
- ***Following the marketing of a drug***, the number of the treated patients increases by several orders of magnitude

Post-marketing surveillance

- The new drugs remain under tight control following their marketing authorisation.
- **Spontaneous reporting of adverse events is *the obligation of every physician, pharmacists!!***
- It is the most effective way for collecting rare adverse reactions



PMS: postmarketing surveillance

Definitions of adverse drug reactions

WHO

„A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis and therapy of disease, or for modification of p hysiological functions„

Definition proposed by Edwards and Aronson (Lancet 2000; 356: 1255-59):

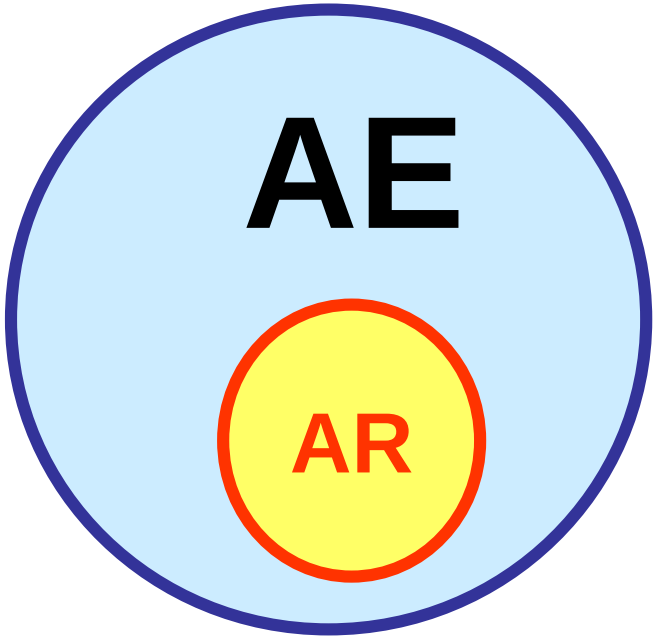
"An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product„

Other aspects of adverse drug effects and reactions

- The definition of the term "adverse reaction" should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of marketing authorisation, including the misuse and abuse of the medicinal product
- Adverse reaction and adverse effect represent two sides of the same reaction
  - An **adverse effects** is seen from the point of view of the drug
  - An **adverse reaction** is seen from the point of view of the patient

Adverse events (AE)-Adverse Reaction (AR)

- **Adverse event (AE):** physical and psychological symptoms of the patients which may or may be not related to the trial drug.
- **Adverse reaction:** a response to the medicinal product which is noxious and unintended. Includes overdose, misuse, abuse and medication errors. The causal realtionship connection of signs and symptoms to the drug is suspected or established
- **Side effect:** an inaccurate term used in medical practice which includes both definitions



Reporters:
- Healthcare professionals
- Patients

Classification of ARs (Edwards & Aronson. Lancet. 2000;356: 1255-59)

Type of reaction	Mnemonic	Features	Examples
A: Dose-related	Augmented	• Common • Related to a pharmacological action of the drug • Predictable • Low mortality	• Toxic effects: Digoxin toxicity; serotonin syndrome with SSRIs • Side effects: Anticholinergic effects of tricyclic antidepressants
B: Non-dose-related	Bizarre	• Uncommon • Not related to a pharmacological action of the drug • Unpredictable • High mortality	• Immunological reactions: Penicillin hypersensitivity • Idiosyncratic reactions: Acute porphyria Malignant hyperthermia Pseudoallergy (eg, ampicillin rash)
C: Dose-related and time-related	Chronic	• Uncommon • Related to the cumulative dose	• Hypothalamic-pituitary-adrenal axis suppression by corticosteroids
D: Time-related	Delayed	• Uncommon • Usually dose-related • Occurs or becomes apparent some time after the use of the drug	• Teratogenesis (eg, vaginal adenocarcinoma with diethylstilbestrol) • Carcinogenesis • Tardive dyskinesia
E: Withdrawal	End of use	• Uncommon • Occurs soon after withdrawal of the drug	• Opiate withdrawal syndrome • Myocardial ischaemia (β-blocker withdrawal)
F: Unexpected failure of therapy	Failure	• Common • Dose-related • Often caused by drug interactions	• Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers

Practical approach for the assessment of AEs

Karch and Lasagna: JAMA, 234: No 12, 1975

Definite: a reaction that

- follows a reasonable temporal sequence from drug administration and occurs at a time when in the organism an effective drug level may be assumed
- follows the known response pattern to the drug
- is confirmed by **dechallenge** on stopping the drug administration and by *reappearance of the reaction on repeated exposure* ***(rechallenge)***

Practical approach for the assessment of AEs

Karch and Lasagna: JAMA, 234: No 12, 1975

Probable: a reaction that

- follows a reasonable temporal sequence from administration of the drug when in the organism an effective drug level may be assumed
- follows the known response pattern to the drug
- is confirmed by dechallenge on stopping the drug administration and that cannot be satisfactorily explained by the clinical condition of the patient

Practical approach for the assessment of AEs

Karch and Lasagna: JAMA, 234: No 12, 1975

Possible: a reaction that

- follows a reasonable temporal sequence from administration of the drug when in the organism an effective drug level may be assumed
- follows the known response pattern to the drug
- but could be explained by the characteristics of the patient's clinical condition
- or could readily have been produced by other, concomitant treatments

Doubtful:

any reaction that does not meet the above requirements

Practical approach for the assessment of the causal relationship of AEs

	Time	Other causes	De-challenge	Re-challenge
Definite	+	-	+	+
Probable	+	-	+	?
Possible	+	+	?	
Doubtful	-	+		
Hypothetical*	?	?	?	?
Cannot be evaluated	Not adequate and/or enough information			

***Signal:** new , observation indicating a hitherto not known new AR

Difficulties and pitfalls determining causality

- The Karch & Lasagna as well as the B. Hill criteria are helpful but frequently are not enough for determining causal relationships. They are most useful for the assessment of **acute toxicities**.The clarification of late ASs are much more complicated.
- Bredford Hill: "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non." …„For stating causality many additional factors should be considered. The required amount of evidence for a causal effect should depend on the possible consequencies of interventions derived from causal conclusions The environment and disease: Association or causation? (Proc Roy Soc Med. London , 1965, 58:295-300)
- Rothman and Greenland: „Causal inference in epidemiology is better viewed as an exercise in measurement of an effect rather than as criterion-guided process for deciding whether an effect is present or not." (Modern Epidemiology 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 1998.)

Further considerations proposed by Bredford Hill for evaluating causal associations

Austin Bradford Hill, "The Environment and Disease: Association or Causation?," *Proceedings of the Royal Society of Medicine*, 58 (1965), 295300.

***Höfler M.,* Emerging *Themes in Epidemiology*20052:11; DOI: 10.1186/1742-7622-2-11**

Counterfactual, or potential outcome model of causality

1. **Strength of association:** A strong association is more likely to have a causal component than is a modest association
2. **Consistency:** A relationship is observed repeatedly
3. **Specificity:** A factor influences specifically a particular outcome or population
4. **Temporality:** The factor must precede the outcome it is assumed to affect
5. **Biological gradient:** The outcome increases monotonically with increasing dose of exposure or according to a function predicted by a substantive theory
6. **Plausibility:** The observed association can be plausibly explained by substantive matter (e.g. biological) explanations
7. **Coherence:** A causal conclusion should not fundamentally contradict present substantive knowledge
8. **Experiment:** Causation is more likely if evidence is based on randomised experiments
9. **Analogy:** For analogous exposures and outcomes an effect has already been shown.

Main categories of the CTC

- Allergy/immunology
- Auditory/hearing
- Blood/bone marrow
- Cardiovascular (arrhythmia)
- Cardiovascular (general)
- Coagulation
- Constitutional symptoms
- Dermatology, skin
- Endocrine
- Gastrointestinal
- Hemorrhage
- Hepatic
- Infection/ febrile neutropenia
- Lymphatics
- Metabolic/laboratory
- Musculoskeletal
- Neurology
- Ocular/visual
- Pain
- Pulmonary
- Renal/genitourinary
- Secondary malignancy
- Sexual, reproductive function
- Syndromes (not included into previous categories)

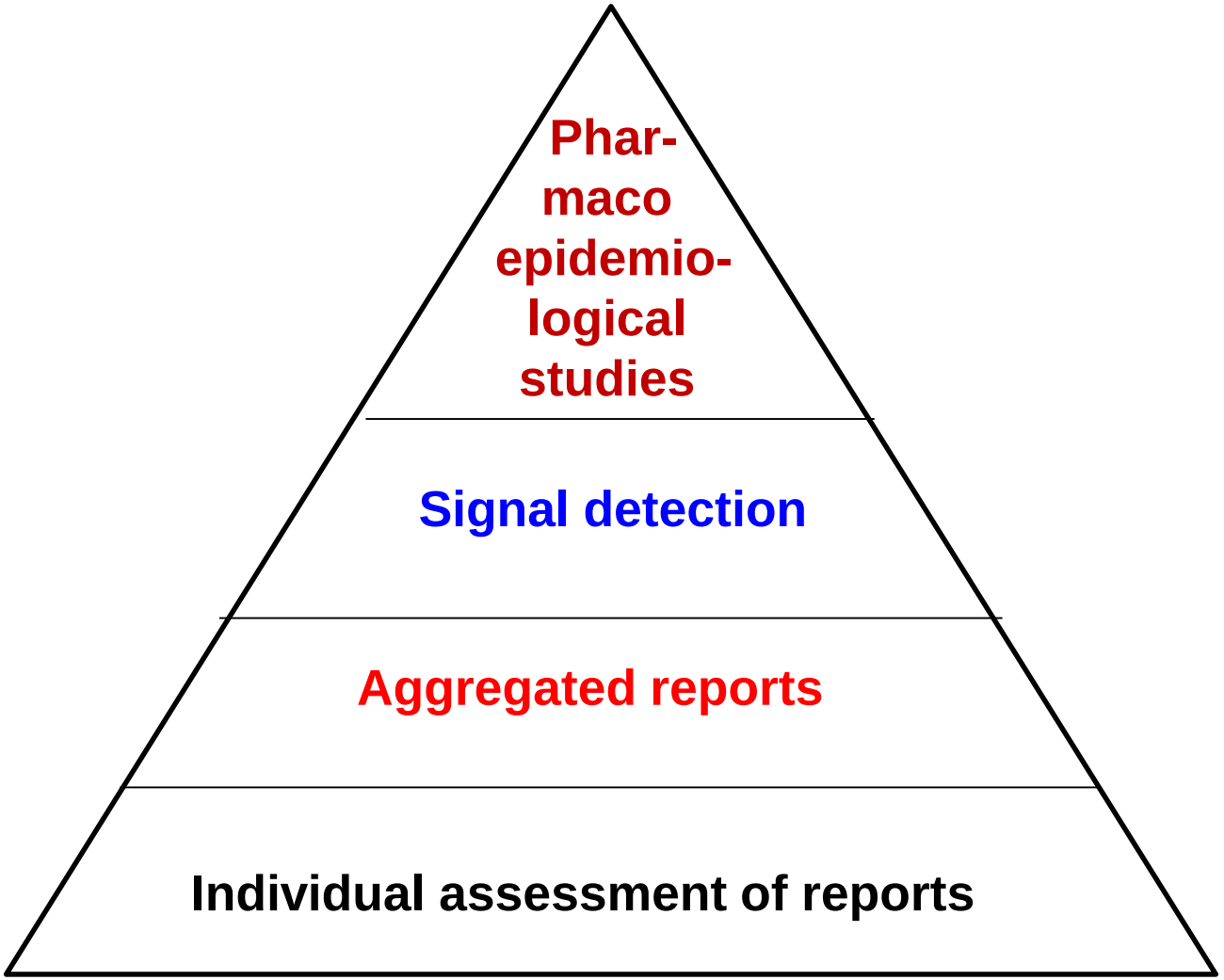
NCI: Common toxicity criteria (CTC)

http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf

CTC Version 2.0
Publish date: April 30, 1999

Adverse event	Toxicity grade				
	0	1	2	3	4

Further evaluation of adverse event reports



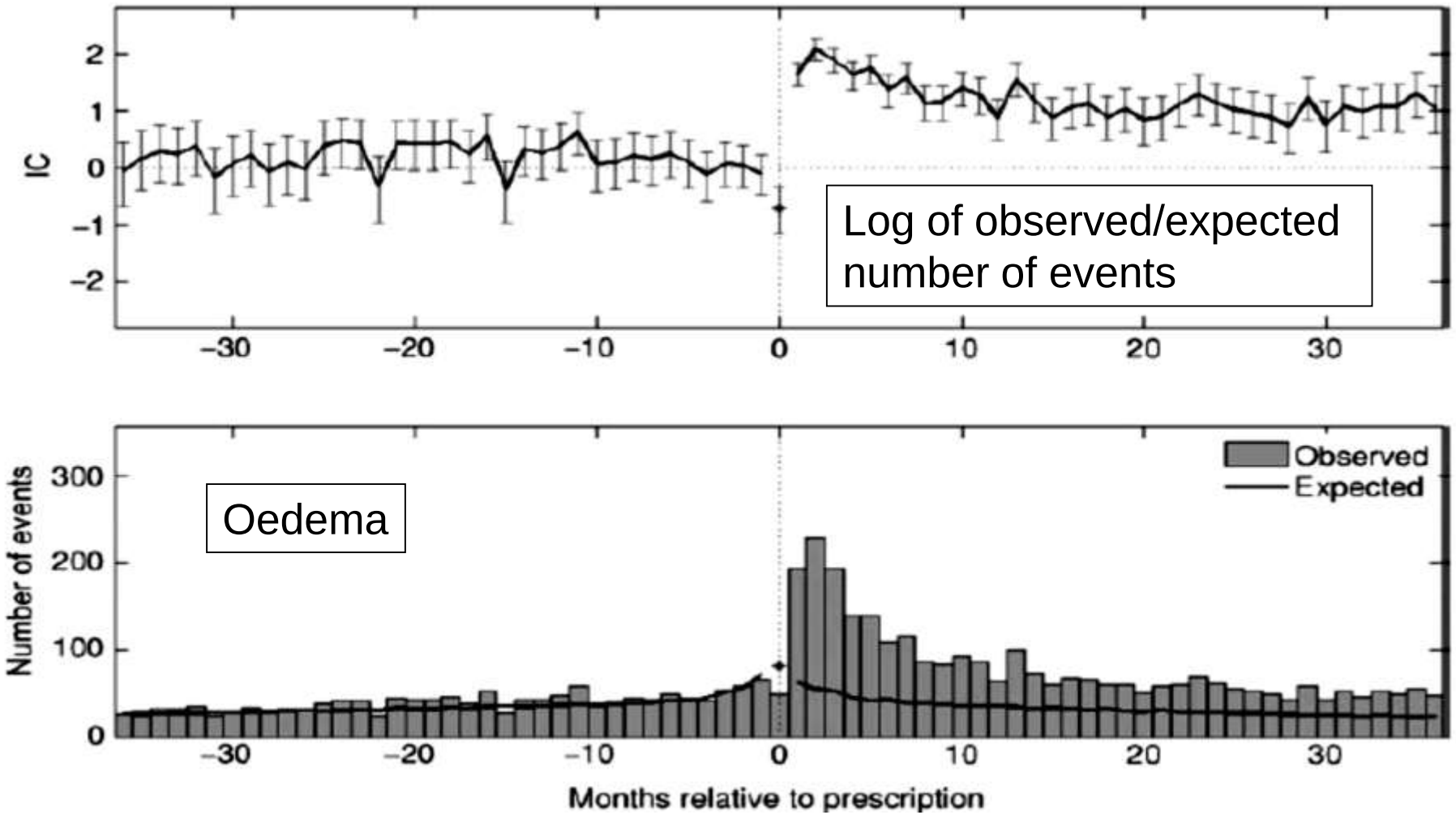
Regulation (EC) No 520/2012 on the performance of pharmacovigilance

- **Signals** are information arising from observations including also experiements which suggests a new potentially causal association either adverse or beneficial which is judged to need verificatory action

- **Evidentiary value** of signals is evaluated based on
  - Nature and quality of data
  - Clinical relevance
  - Strength of the association
  - Consistency of the data
  - Exposure-response relationship
  - Biological plausibility
  - Experiemental findings
  - Possible analogies

Modern methods of pharmacovigilance

Norén GN & Edwards IR: Clinical Medicne 9:486-489, 2009



Persistent increase of AE reporting subsequent to prescription of Amlodipine in longitudinal electronic patient records.

Some examples

Biological medicnal product

Clinical consequences of immunogenicity

Biological medicine
(protein)

Antibody production

No effect

Neutralizing Abs
Decreased clinical efficacy

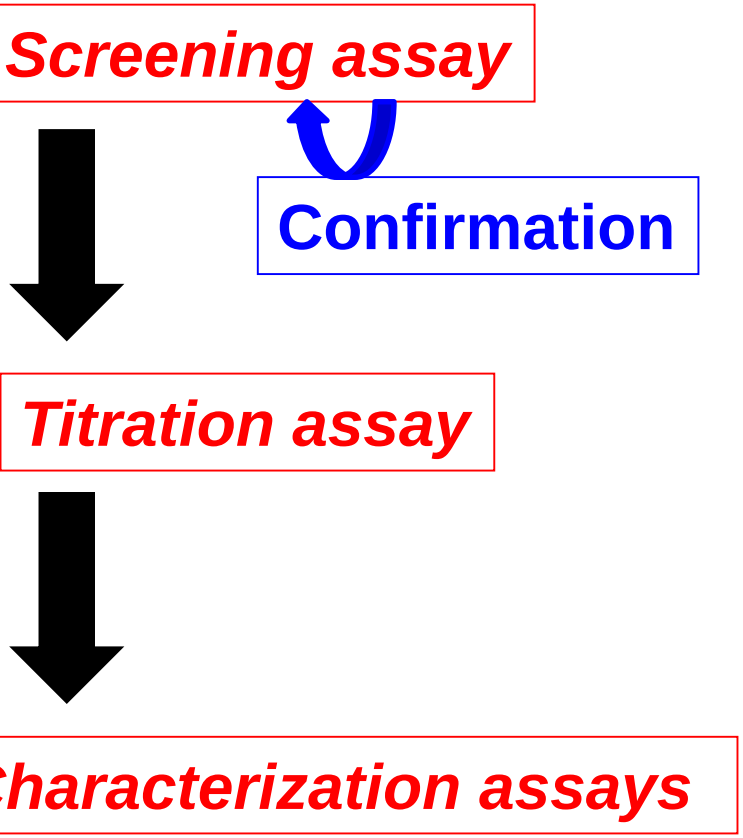
Pharmacokinetic differences
Bioequivalence studies might be interfered with

Neutralization of native proteins
Impairment of physiological functions

Characterization of antibodies developed

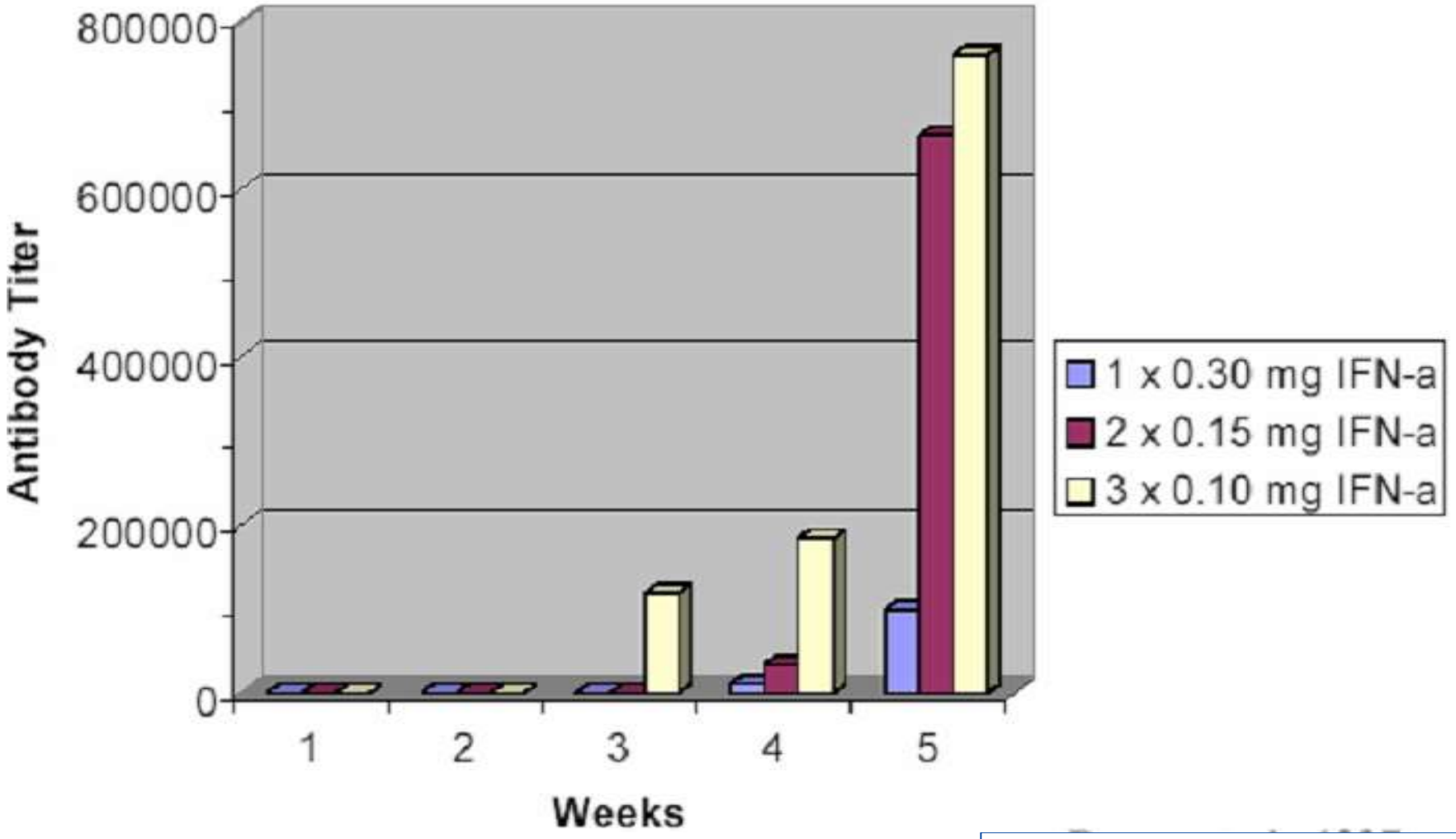
Courtesy of Stanulovic V.

- Screening assay
- Confirming assay
  - Confirmation of positive assay with excess drug
- Titer determination
- Characterization assays
  - Neutralization of activity / blocking of binding
  - Isotype determination
  - Complement fixing ability
  - Epitope mapping (anti-framework, anti-CDR)
  - Determination of relative binding affinity



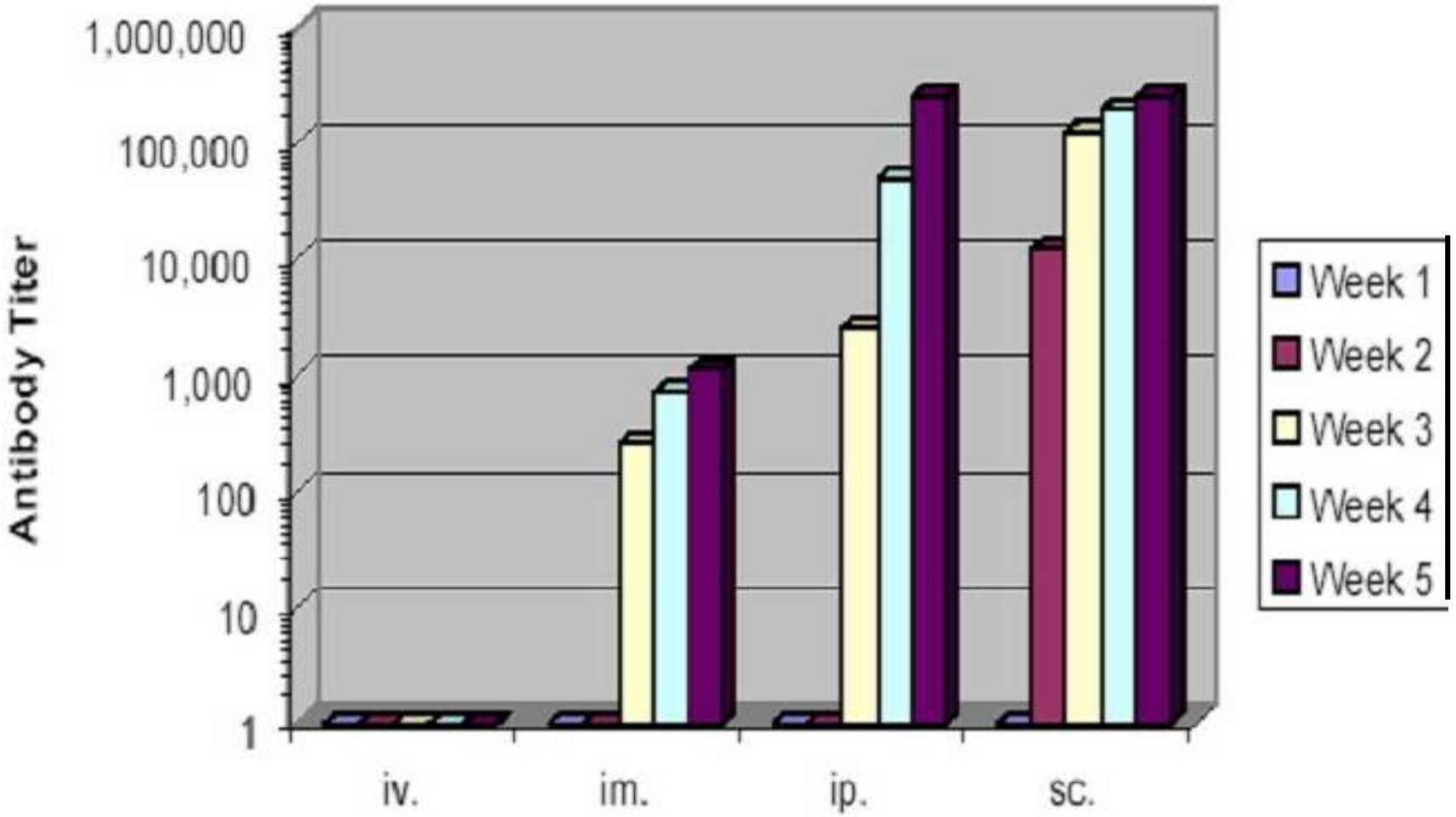
Antibody formation in relation to the frequency of administration

Braun et al. Pharm. Res. 14:1472, 1997

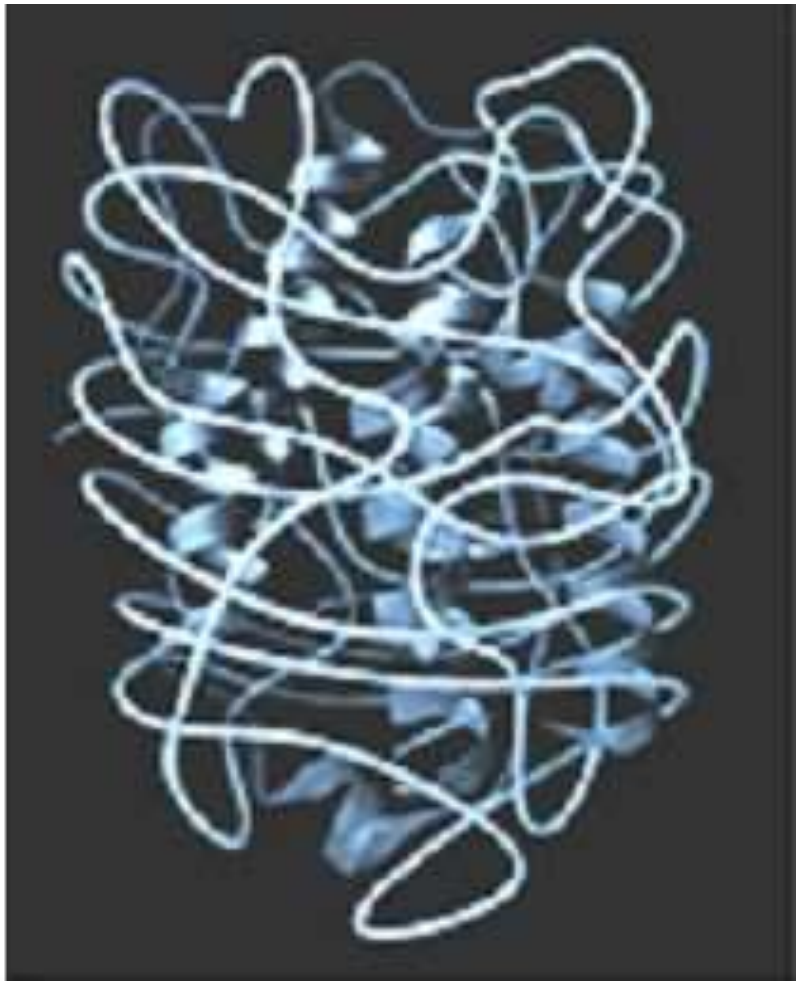


Antibody formation in relation to the administration sites

Braun et al. Pharm. Res. 14:1472, 1997



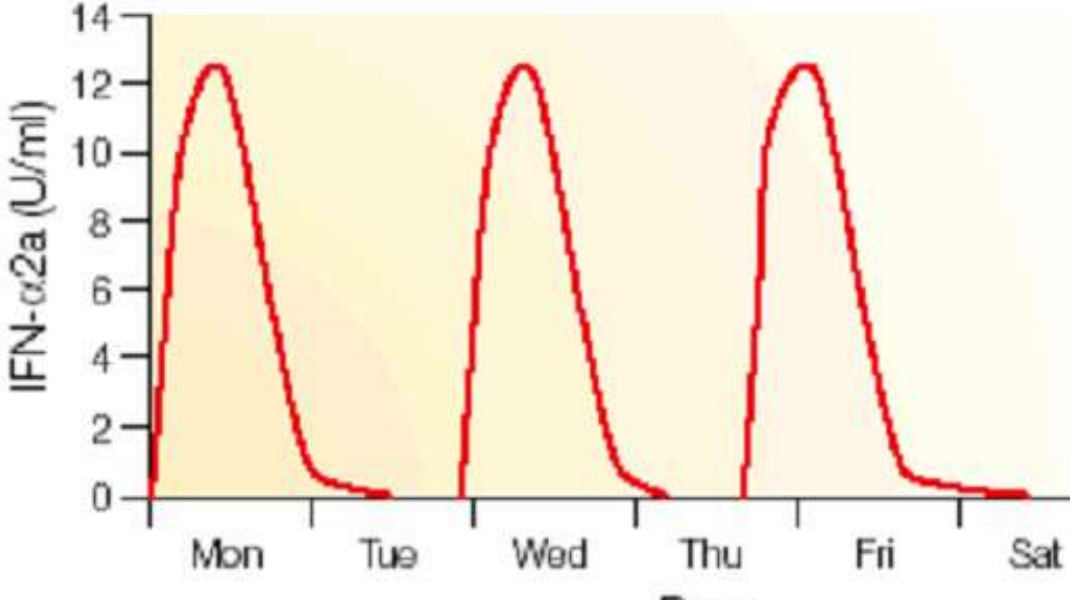
Pegylation of proteins



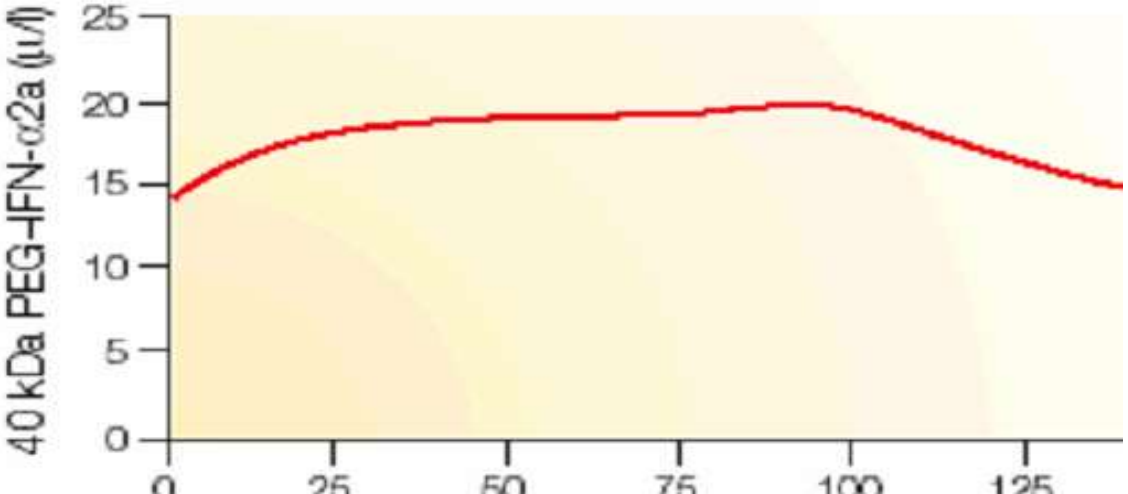
Pegylation increases stability of proteins, prolongs circulation time due to decreased kidney secretion and decreases immunogenicity

Pharmacokinetic characteristics of IFN-α 2a and PEG-IFN-α 2a

Harris JM and Chess RB. Nat Rev DrugDiscov, 2:214, 2003



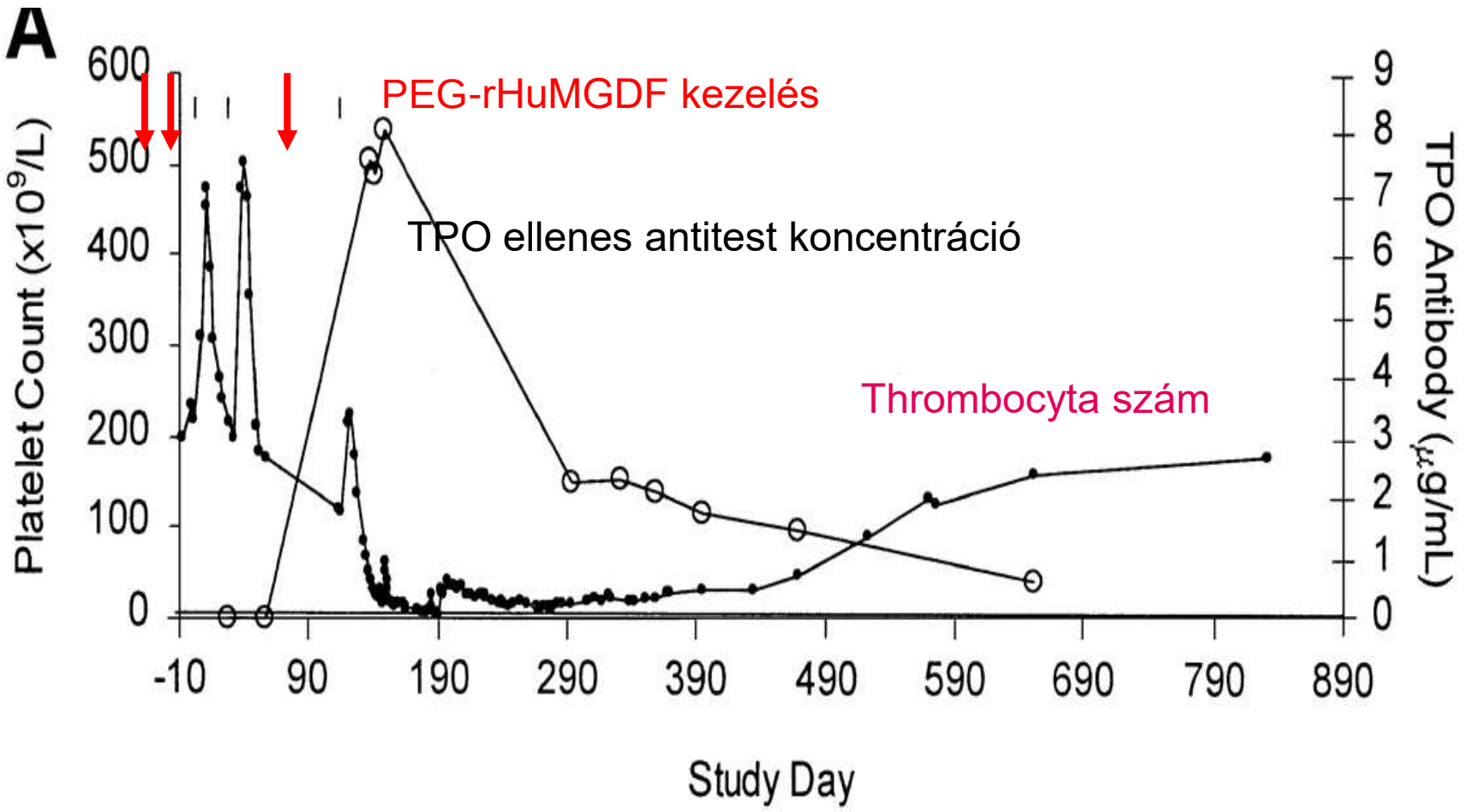
Administration every 2nd day



Weekly administration PEG40(kDA) IFN-α 2a

Neutralizáló antitestek által kiváltott thrombocytopenia

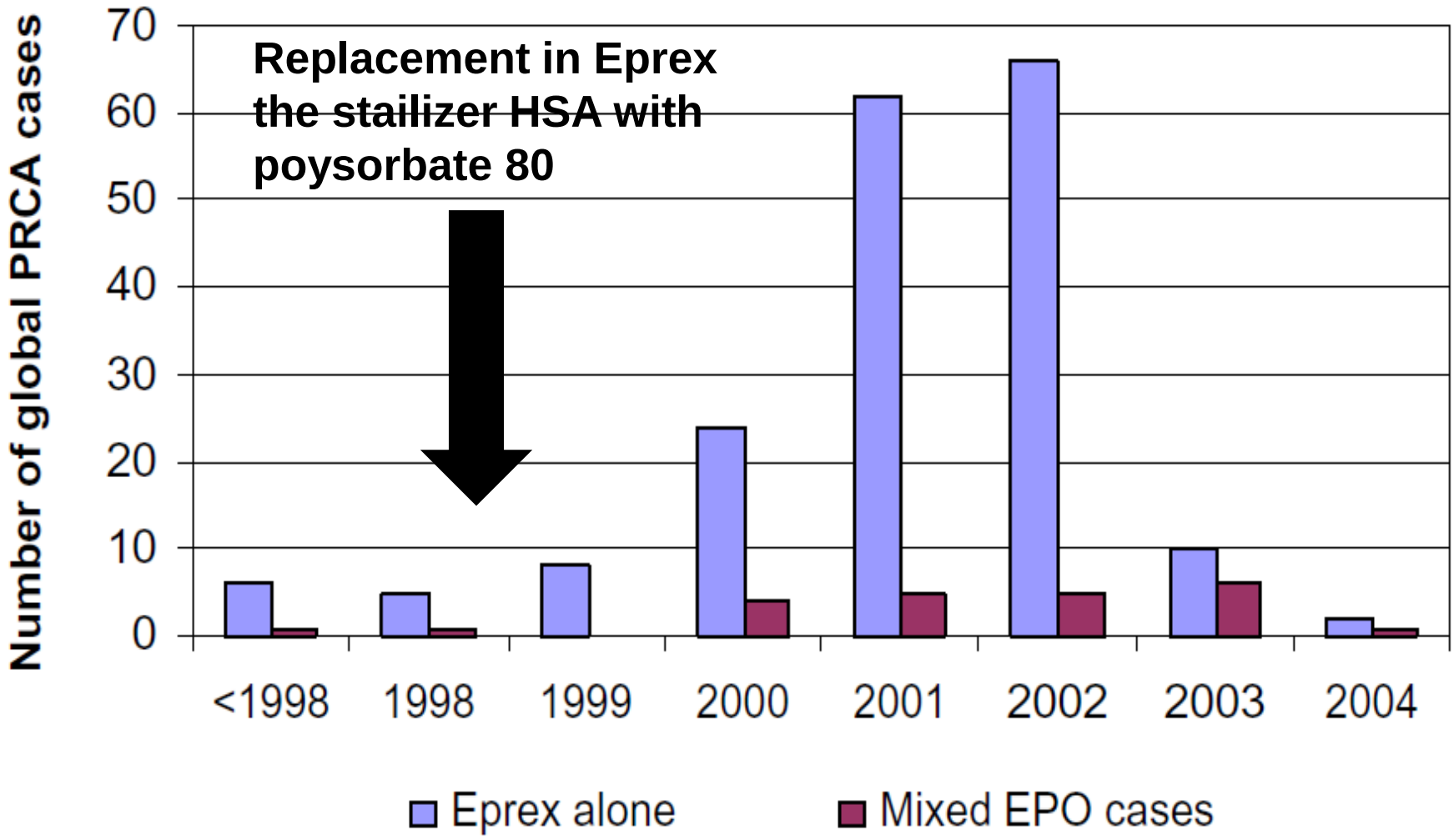
Chun JL et al. Blood, 98:3241-3248. 2001



- Pegilált-rekombináns-humán-megakaryocyta-growth and development faktor.

Gloabal case numbers of antibody-mediated Pure Red Cell Aplasia (PRCA) [k]

McDougall Nephrol Dial Transplant, 20 (Suppl 4) 9-15 2005; doi:10.1093/ndt/gfh1087



PRCA Worldwide Exposure–Adjusted Incidence between 2001-2003

Bennett CL, Luminari S, Nissenson AR, Tallman MS, Klinge SA, et al. Pure red-cell aplasia and epoetin therapy. N Engl J Med. 2004 Sep 30;351(14):1403-8

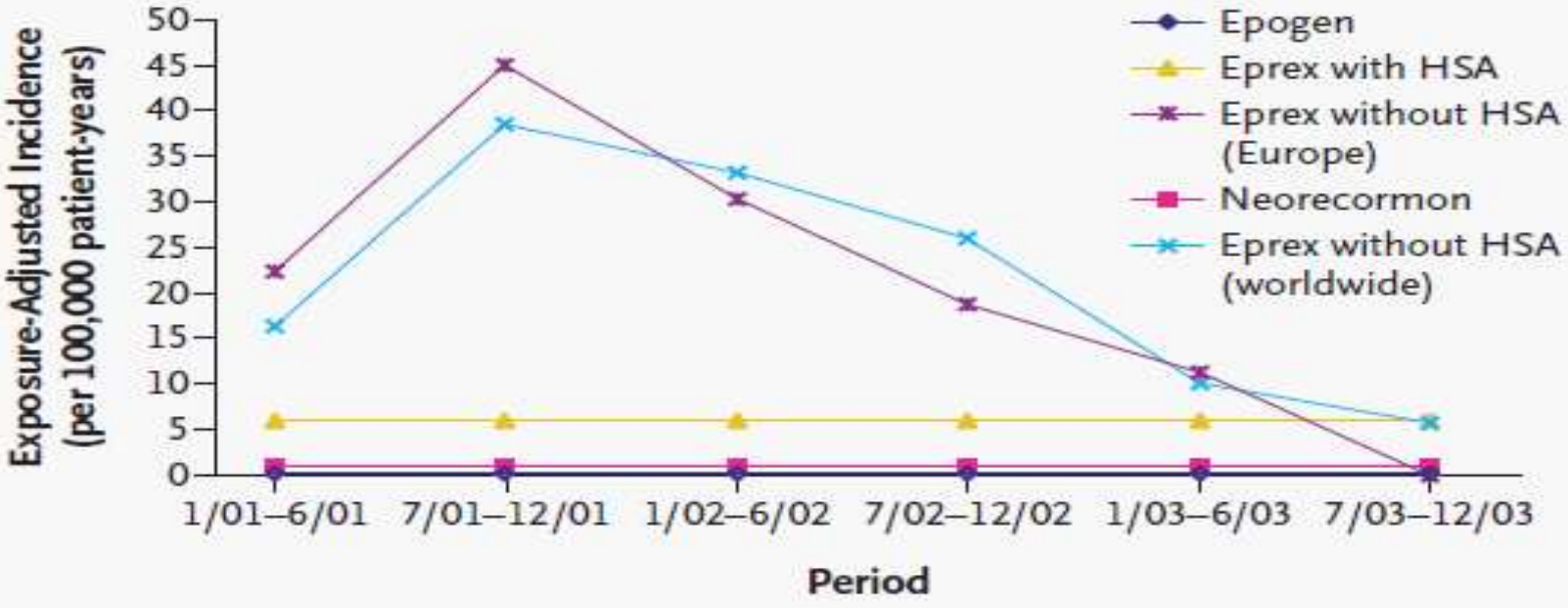


Figure 2. Estimates of the Worldwide Exposure-Adjusted Incidence of Epoetin-Associated Pure Red-Cell Aplasia According to the Product, between January 1, 2001, and December 31, 2003.

HSA denotes human serum albumin. Epogen is also marketed as Procrit, and Neorecormon as Recormon.

Changing Frequency of Adverse Reaction

Bennett CL, Luminari S, Nissenson AR, Tallman MS, Klinge SA, et al. Pure red-cell aplasia and epoetin therapy. N Engl J Med. 2004 Sep 30;351(14):1403-8

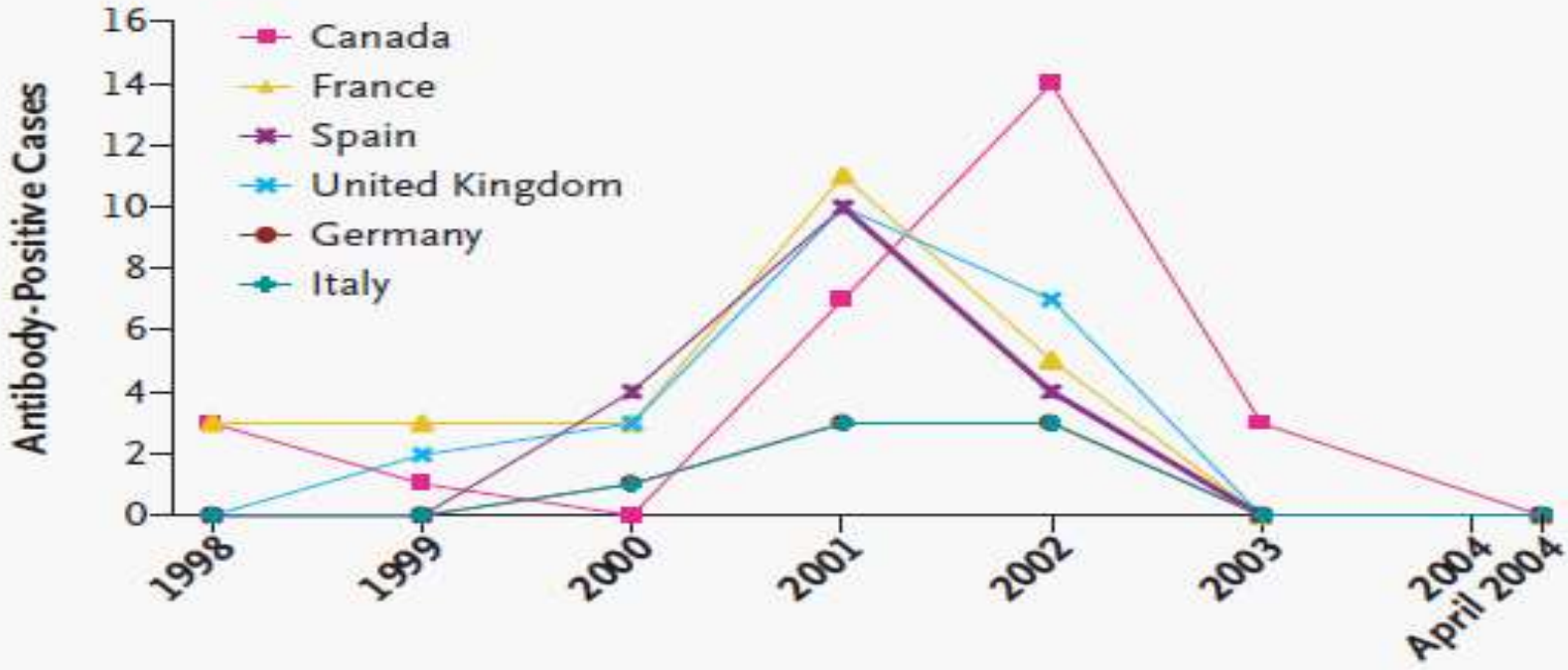
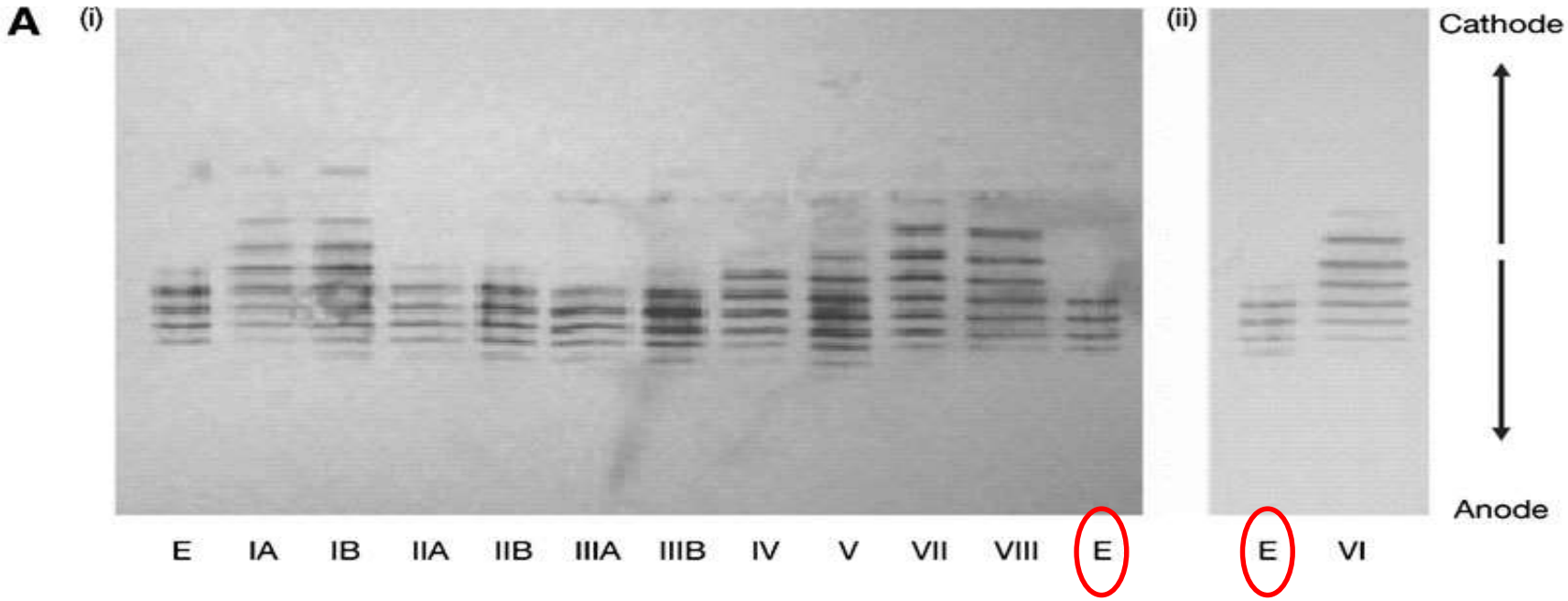


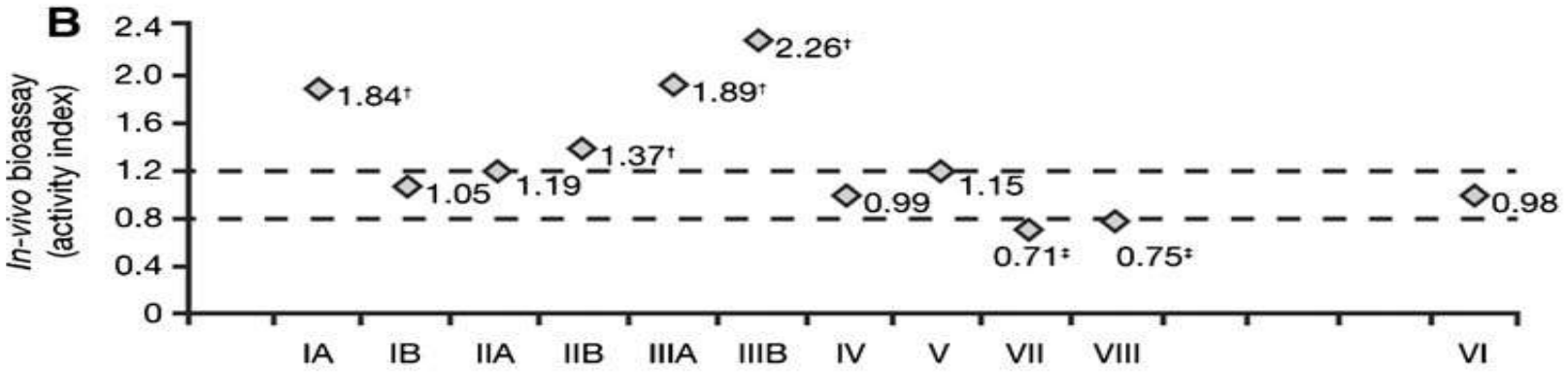
Figure 1. Cases of Antibody-Positive, Eprex-Associated Pure Red-Cell Aplasia Identified in the Database of the Adverse Event Reporting System of the Food and Drug Administration between January 1998 and April 2004.

In Germany and Italy there were the same number of case reports within each year.

The physical-chemical and biological characteristics of epoetins produced outside of US and EU.

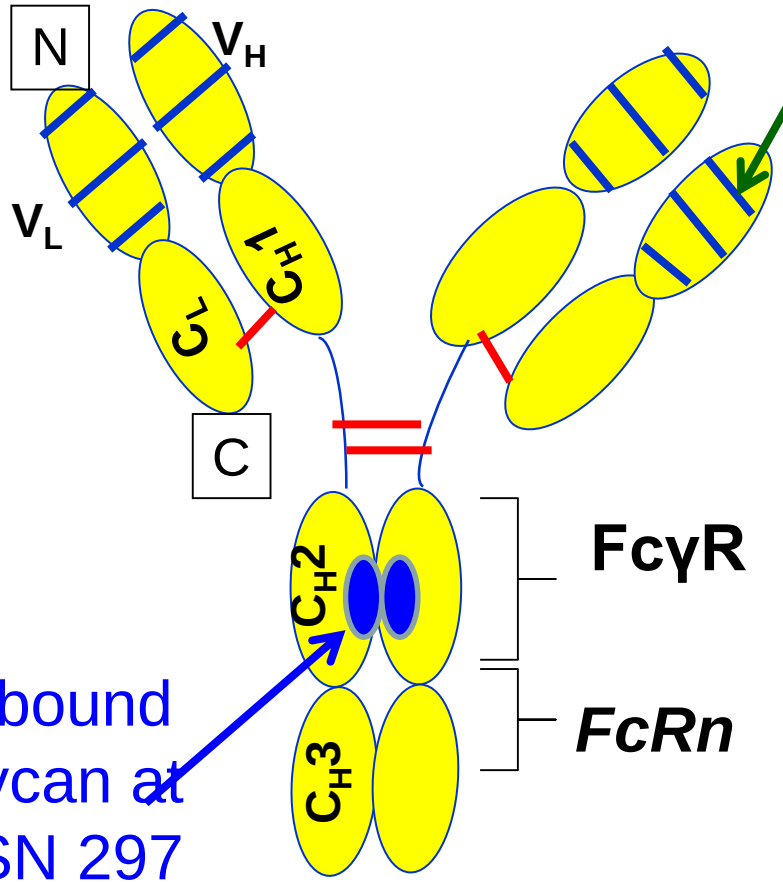
Schellekens H, NDT Plus (2009) 2 [Suppl 1]: i27–i36; doi: 10.1093/ndtplus/sfn177





Specified activity range

IgG: complex and multifunctional molecule



Complementarity determining regions (CDR)

Antigen binding

Direct effects due to Fab (eg. apoptosis)

ADCC
CDC
ADCP
functions

FcγR

FcRn

Pharmacokinetical characteristics

N-bound glycan at ASN 297 locus

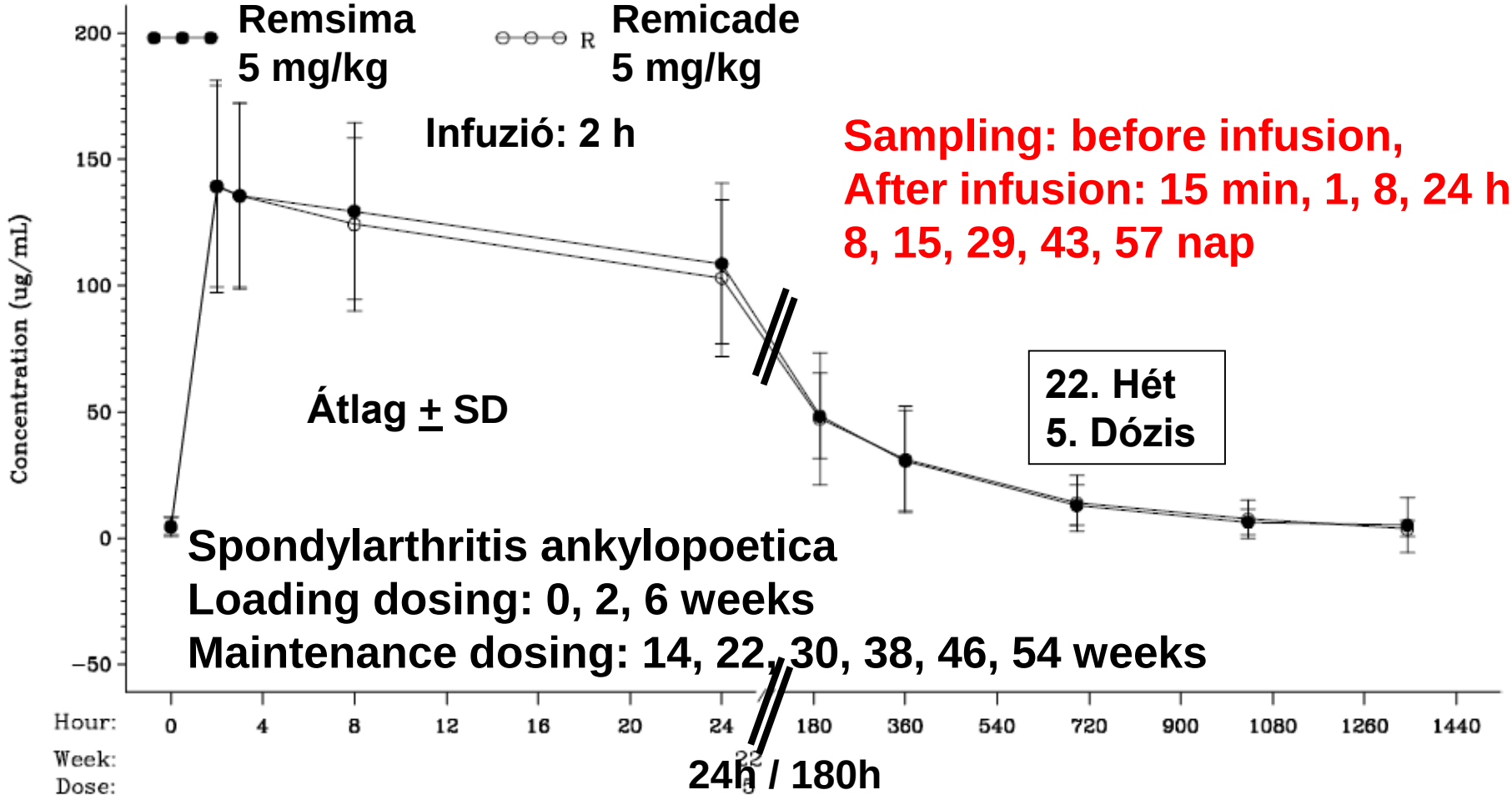
Comparative *in vitro* evalaution of the biological effects of Remsima and Remicade (infliximab)

Remsima EPAR, EMA/CHMP/589317, 2013

FCγR I, FCγR IIa, b, FcRn (SPR: Surface Plasmon Resonance)	Similar binding affinityies
FCγR IIIa, b (SPR)	Remsima: lower binding affinity to both receptors
Ex vivo FCγR IIIa, b binding to NK and neutrofil cells derived from healthy volunteers and CD patients	Lower affinity to NK cell FCγR IIIa, b receptors. (V/V, V/F genotypes; F/F genotypes no difference. Addition of sera derived from CD patients abolished the difference. In neutrofil cells do differences were observed
hTNFα és tm hTNFα binding (ELISA; SPR))	Similar binding affinities
Binding to human tissues (IH)	Similar
hTNFα neutralization test on hTNFα sensitive cells	Similar dose ranges and similar activities
Complement dependent cytotoxicity (CDC)	Similar
Antibody dependent cell mediated cytotoxicity (ADCC)	Similar

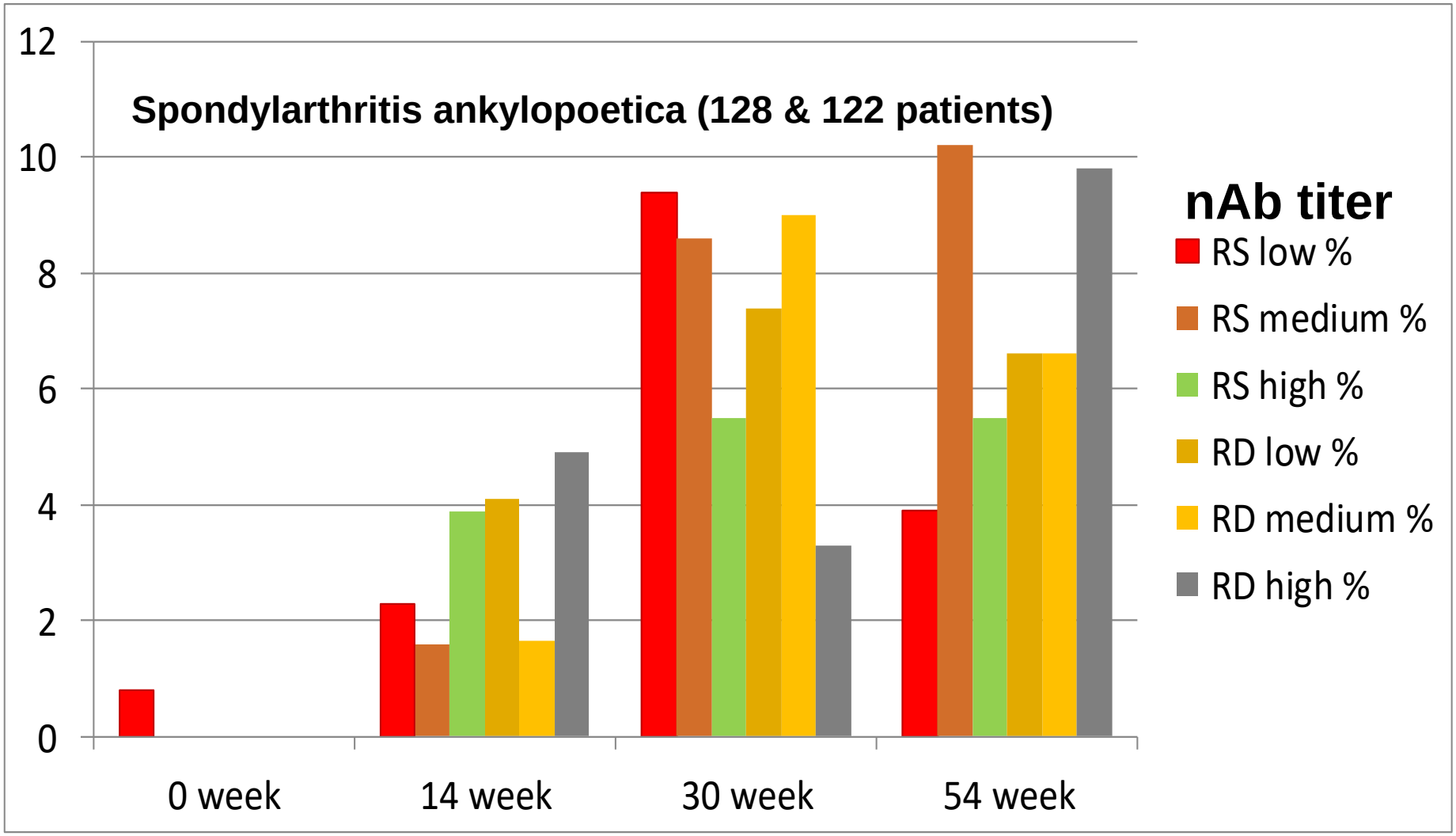
Comparative pharmacokinetic evalauation of Remsima and Remicade (infliximab)

REMSIMA: EPAR, EMA/CHMP/589317/2013



The appearence of neutralizing antobodies (nAb) during treatment with Remsima (RS)&Remicade (RD)

Remsima EPAR, EMA/CHMP/589317, 2013



Remsima & Remicade (infliximab) comparative clinical efficacy in RA

REMSIMA: EPAR, EMA/CHMP/589317/2013

Hatás	Remsima (%)	Remicade (%)	Kezelési különbség	95% CI
(14 hét) ACR 20	180/248 (72,6)	164/251 (65,3)	0,07	-
ACR 50	98/248 (39,5)	85/251 (33,9)	0,06	-
ACR 70	41/248 (16,5)	34/251 (13,5)	0,03	-
(30 hét) ACR 20	**182/248 (73,4)**	**175/251 (69,7)**	**0,04**	**(-0,04 - 0,12)**
ACR 50	105/248 (42,3)	102/251 (40,6)	0,02	-
ACR 70	50/248 (20,2)	45/251 (17,9)	0,02	-
(54 hét) ACR 20	168/248 (68,3)	155/250 (62,0)	0,06	-
ACR 50	98/246 (39,8)	94/250 (37,6)	0,02	-
ACR 70	48/246 (19,5)	44/250 (17,6)	0,02	-

The effect of neutralizing antibodies (nAb) on the pharmacokinetic properties of Remsima & Remicade

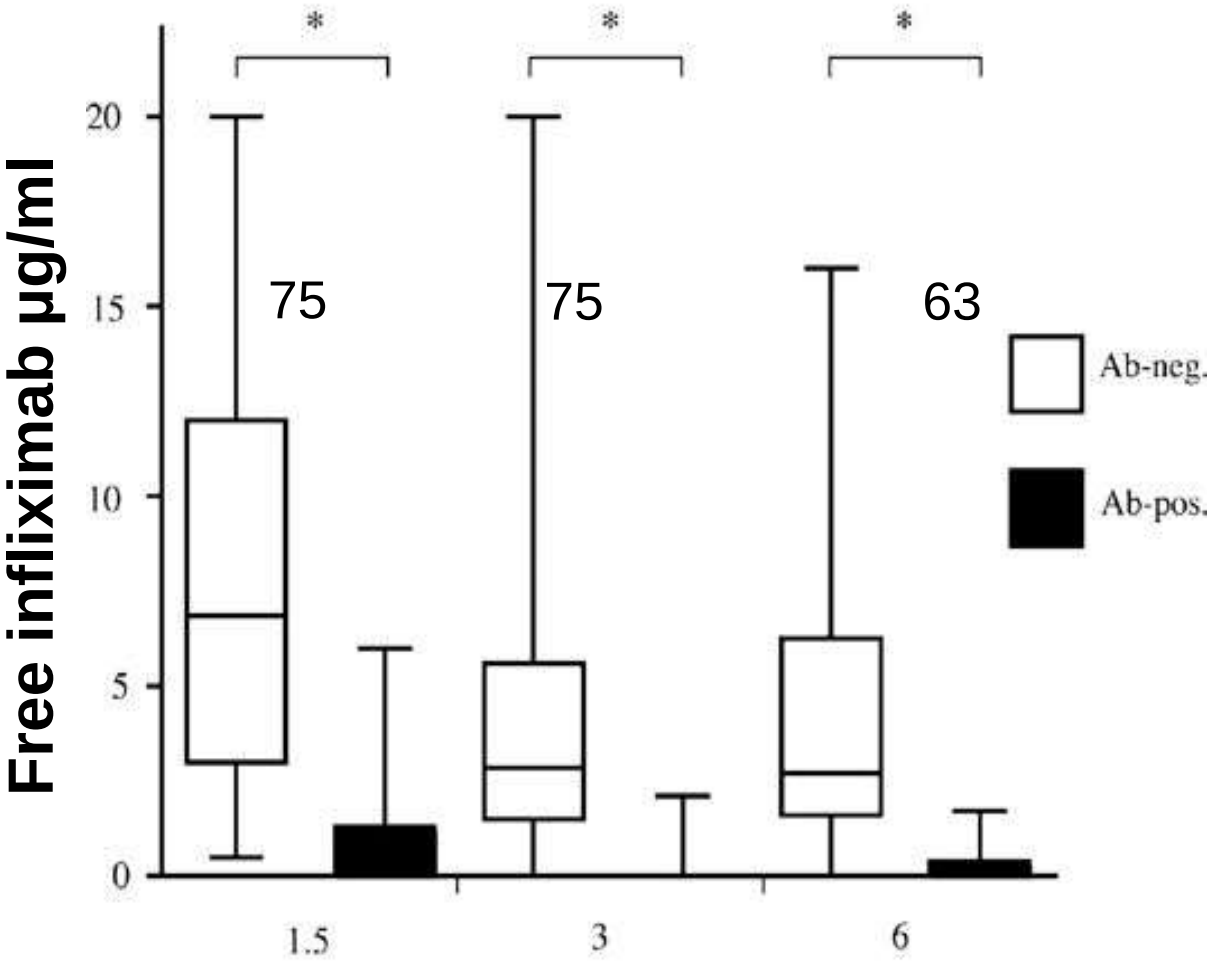
Remsima EPAR, EMA/CHMP/589317, 2013

Parameter	Remsima Geometric mean	Remicade Geometric mean	Quotient of Geometric mean %	90% CI
AUCτ µg/mL * h	37725,5 ***22821,6***	37221,0 ***21313,7***	101,4 ***107,1***	92,5-111,1 ***86,7-131,9***
Cmax,ss µg/mL	152,7 ***133,9***	147,8 ***136,6***	103,3 ***98,0***	95,4-111,9 ***85,1-113,0***
***Cmin,ss µg/mL**	3,7 0,8	3,2 0,6	-	-
***CLss mL/h**	10,1 ***16,2***	10,3 ***20,7***	-	-
***T1/2 h**	310,6 ***193,2***	304,7 ***181,8***	-	-
***Vss mL**	3828 ***3136,5***	3809,8 ***3223,1***	-	-

*Values measured after the 5th dose (112-110 pts)

The clinical significance of anti-infliximab antibodies

Svenson M et al., Rheumatology, 46:1828-1834, 2007



- The free infliximab titers at the time of the minimum values in Ab-positive and Ab-negative patients
- * p< 0.0001

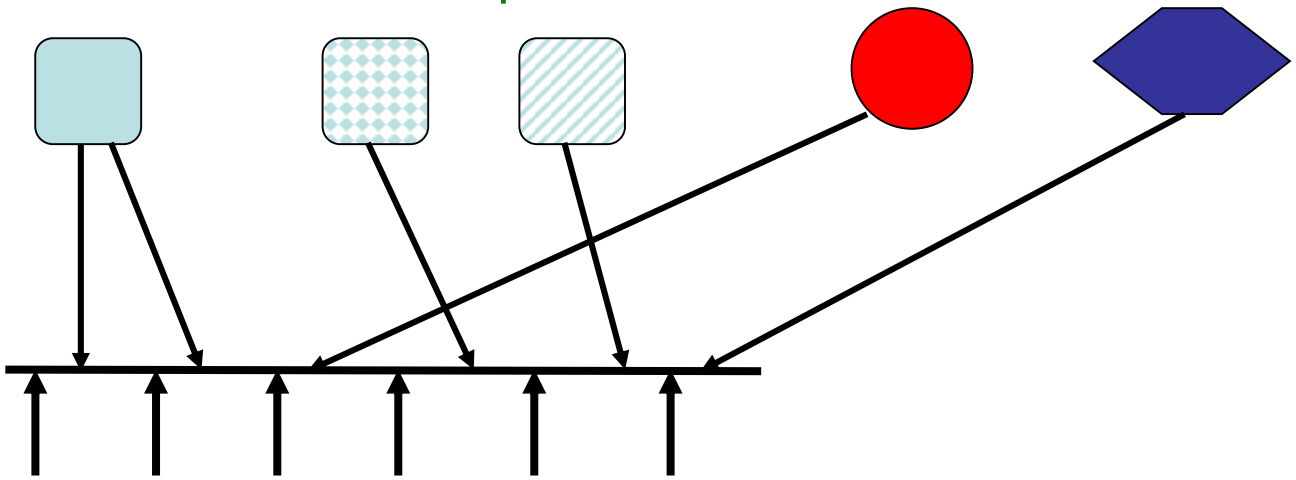
Correct and incorrect clinical application of analogue és biosimilar medicines

Incorrect

Starting medicine of the treatment

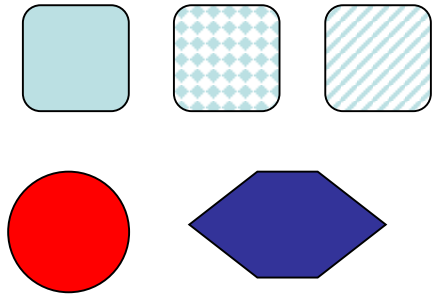
Biosimilar products

Analogue products



Exchange of medicines

Correct



Any of the medicines without replacement

- Exchange of medicines should be done only due to medical reasons and should be followed by intensive monitoring of the patients
- Could the guidance for *medical substituton* of biosimilars with low immunogenicity become more relaxed on the basis of clinical experience?

The application of biological medicinal products in the EU

„Drug fortress European Union”

Marketing authorization

Efficacy, safety, quality

Risk management plan

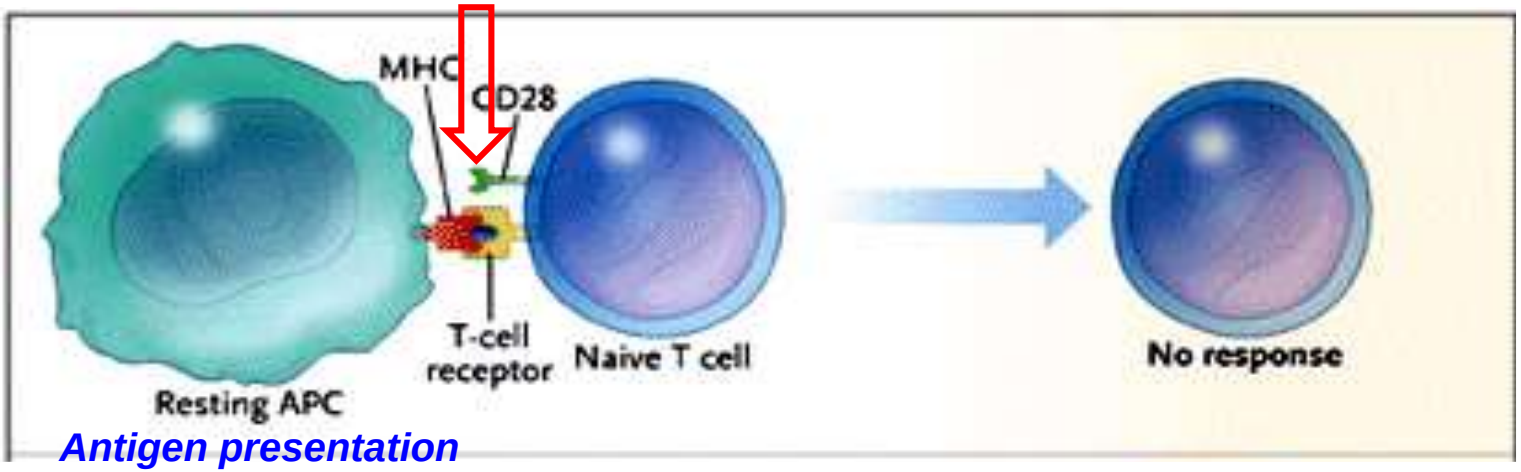
The use of biological medicinal products not registered in the EU is not permitted and additionally might be dangerous

Adverse reactions during phase I human drug development

The TGN1412 study concept

TeGenero Immuno Therapeutics

TGN1412 Superagonist



Antigen presentation

- **TGN1412 Superagonist (https://en.wikipedia.org/wiki/TGN1412)**
- The TCR-independent IgG4 superagonist mAb of CD28 binds to C"D loop of CD28. It was initially hypothesized that this could be therapeutically useful in stimulating the immune system in immunosuppressed patients
- Animal experiments indicated that administration would lead to preferential activation of regulatory T cells, leading to a net effect of T-cell downregulation
- ***However, in humans it caused super stimulation and cytokine storm***

Incorrect FIH dose calculation demonstrating mistakes due to lack of combined approach of toxicology & pharmacology

Sims J:http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500010862.pdf

TGN1412

Toxicology based calculation

NOAEL : 50.0 mg/kg

- Convert NOAEL to HED (16 mg/kg)
  - Adjust for anticipated exposure in man (not done)
  - Adjust for inter-species differences in affinity/potency (not done)
- Apply ≥ 10-fold safety factor

1.6 mg/kg, increased to 160 fold:

0.1 mg/kg) ; ~ 0.95 nM plasma level

= 1/500 of NOAEL

Pharmacology based calculation

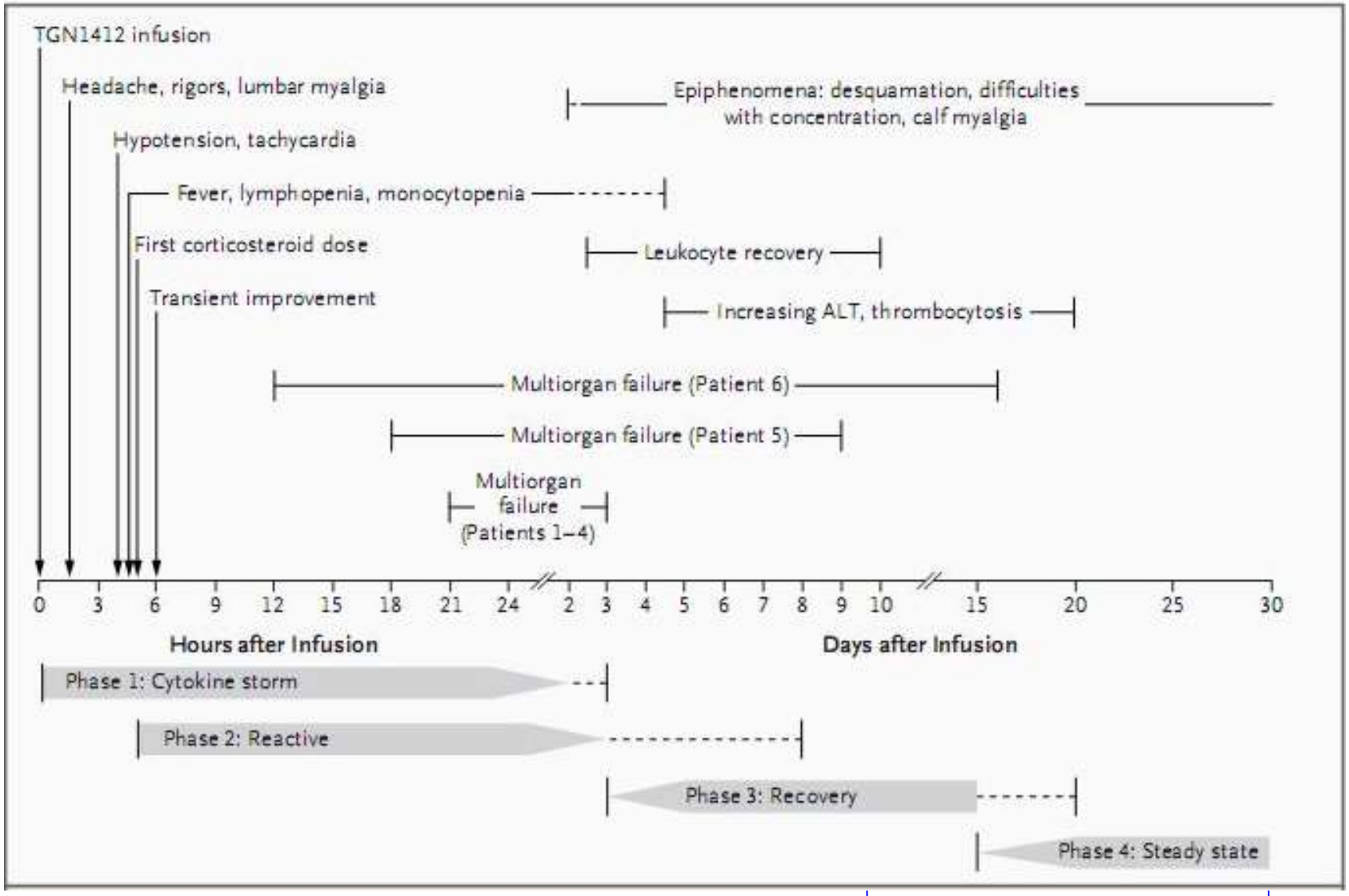
- Estimate MABEL
  - Justify based on pharmacology
  - Adjust for anticipated exposure in man
  - Include anticipated duration of effect
  - Adjust for inter-species differences in affinity/potency

T-cell proliferation (0.1 µg/ml) in vitro with murine anti CD28 (JJ316)

(250µgTGN1412/2500 ml plasma volume results in 0.1µg/ml concentration. (250µg/70 kg~3µg/kg)

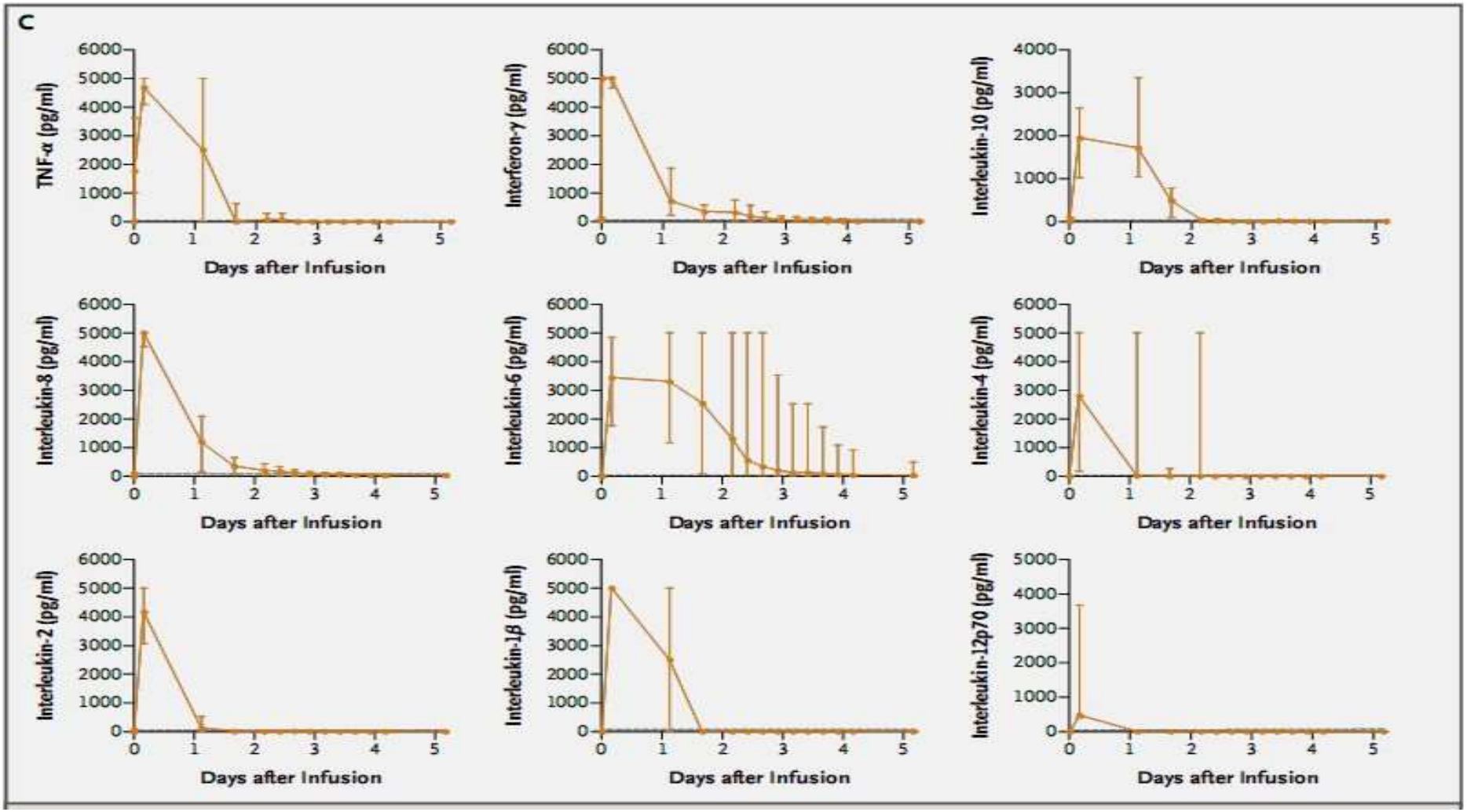
TGN1412- The dynamics of the events

Suntharalingam G et al. NEJM 355:1018, 2006



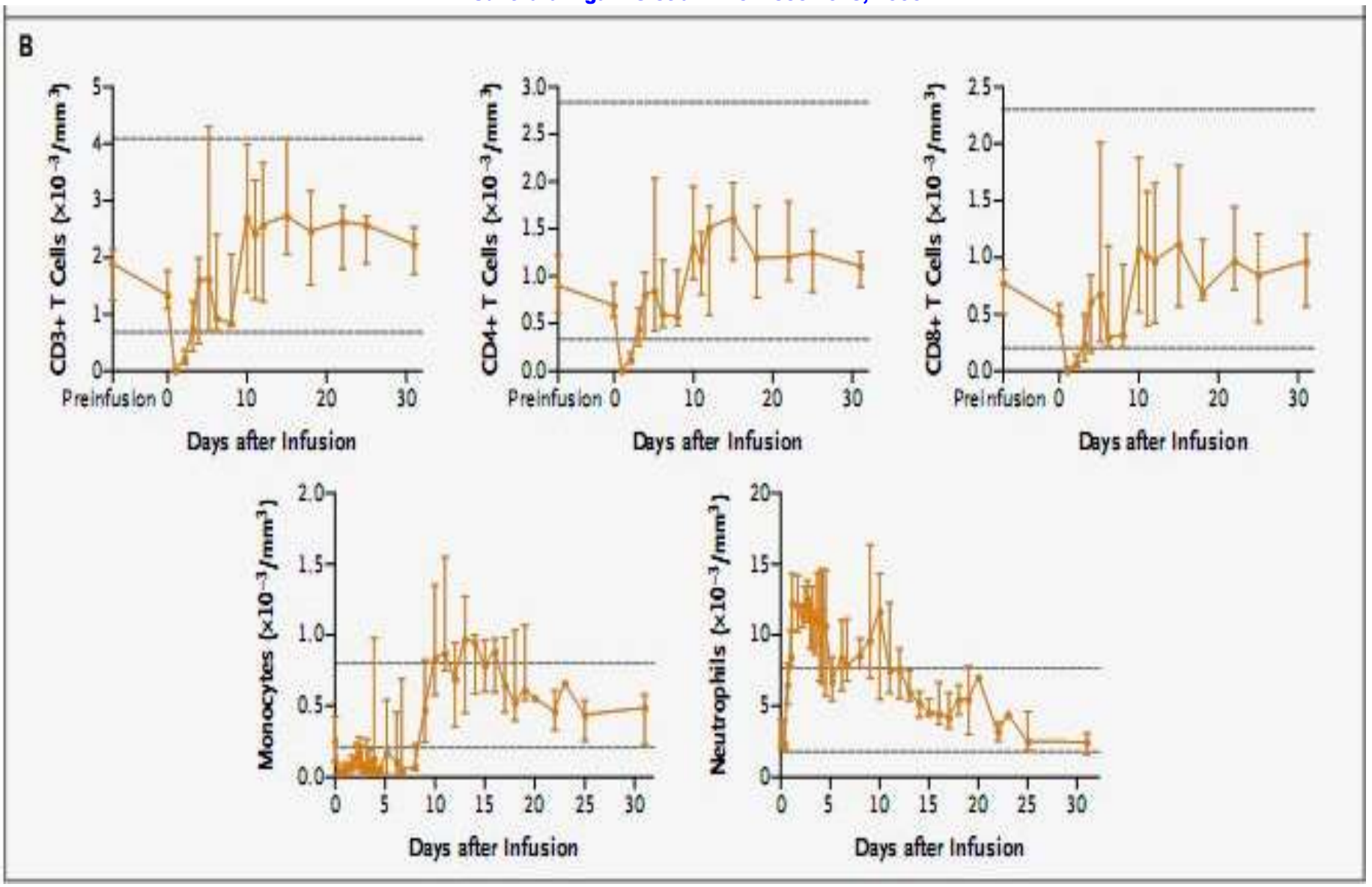
TGN-1412 cytokine storm

Suntharalingam G et al. NEJM 355:1018, 2006



TGN1412 Laboratory results

Suntharalingam G et al. NEJM 355:1018, 2006



Incorrect FIH dose calculation demonstrating mistakes due to lack of combined approach of toxicology & pharmacology

Sims J:http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500010862.pdf

TGN1412

Toxicology

NOAEL : 50.0 mg/kg

- Convert NOAEL to HED (16 mg/kg)
  - Adjust for anticipated exposure in man (not done)
  - Adjust for inter-species differences in affinity/potency (not done)
- Apply ≥ 10-fold safety factor

1.6 mg/kg, increased to 160 fold:

0.1 mg/kg) ; ~ 0.95 nM plasma level

Pharmcology

- Estimate MABEL
  - Justify based on pharmacology
  - Adjust for anticipated exposure in man
  - Include anticipated duration of effect
  - Adjust for inter-species differences in affinity/potency

T-cell proliferation (0.1 µg/ml) in vitro with murine parent to TGN1412 =0.003 mg/kg in man. For 10% receptor occupancy ~0.001 mg/kg

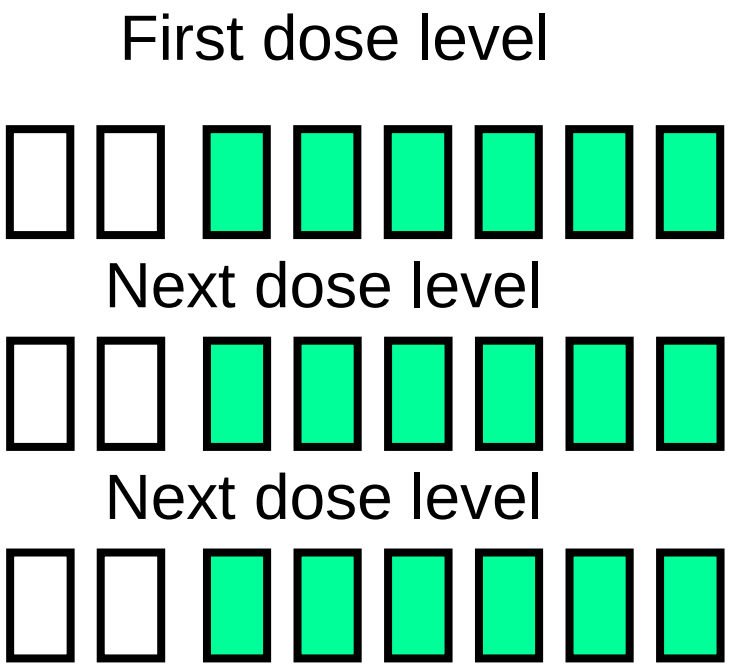
Maximum recommended starting dose

Define anticipated safety window based on NOAEL & MABEL

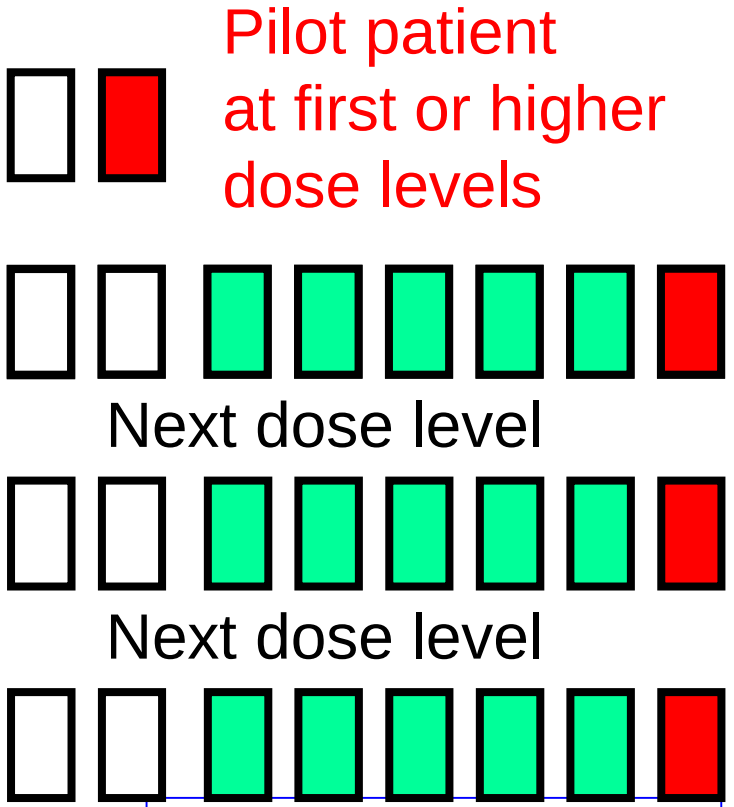
- Appropriate safety factor, if necessary based on potential risk
- **Correct FIH dose: 0.001 mg/kg**

Various dose escalation arrangements

Economic but relatively more dangerous dose escalation scheme

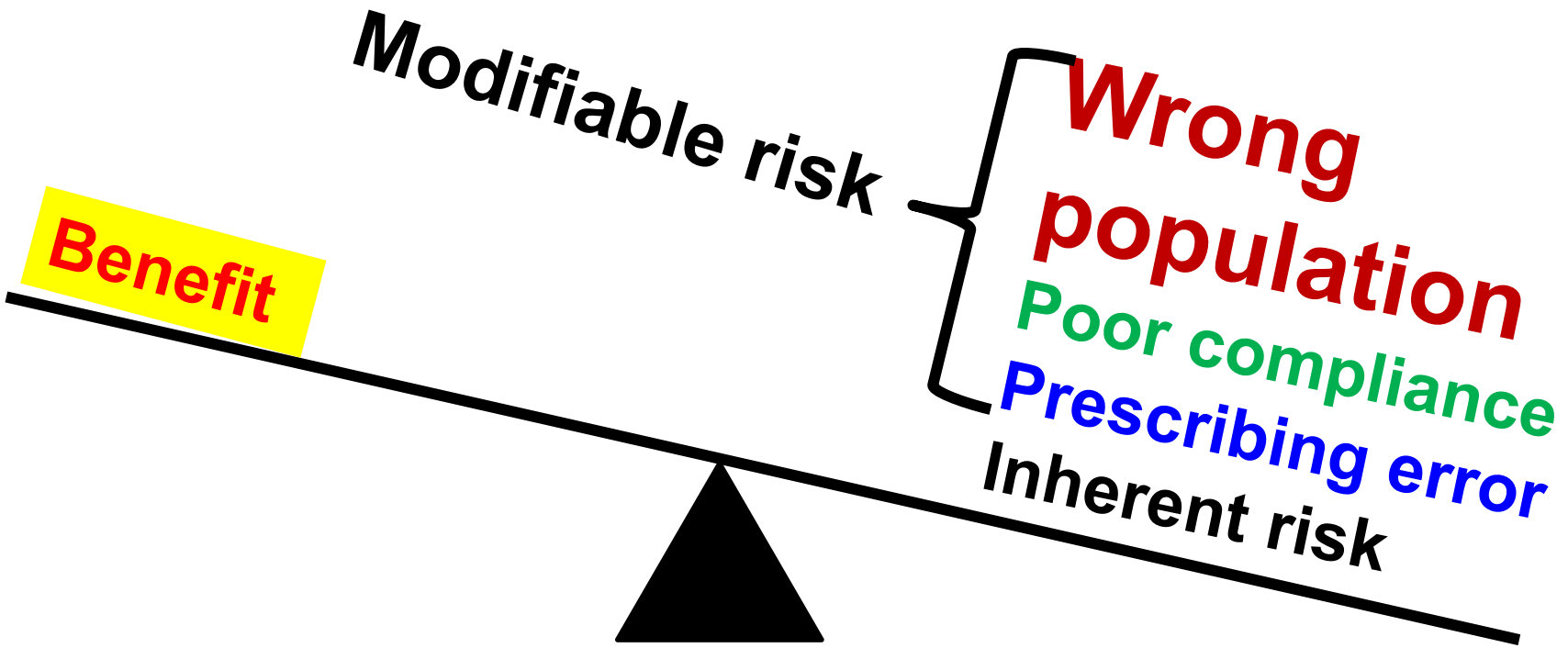


Less economic but safer dose escalation scheme



Adverse drug reactions in pediatric and elderly populations

Dystortion of the benefit-risk equation



Normal adults

Infants

Different body composition

Activities of physiological functions ***develop*** to various extent at various times

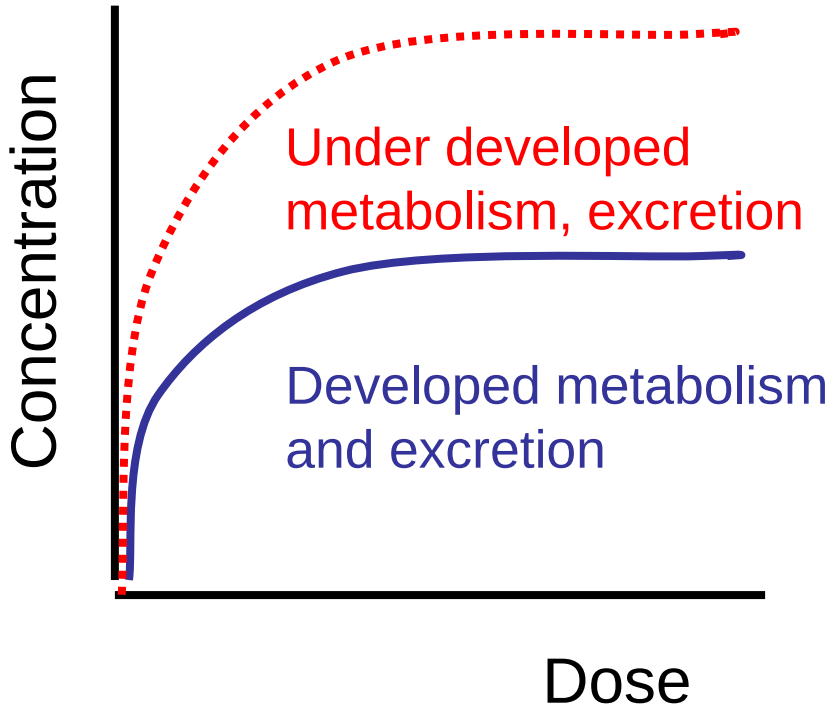
Elderly

Different body composition

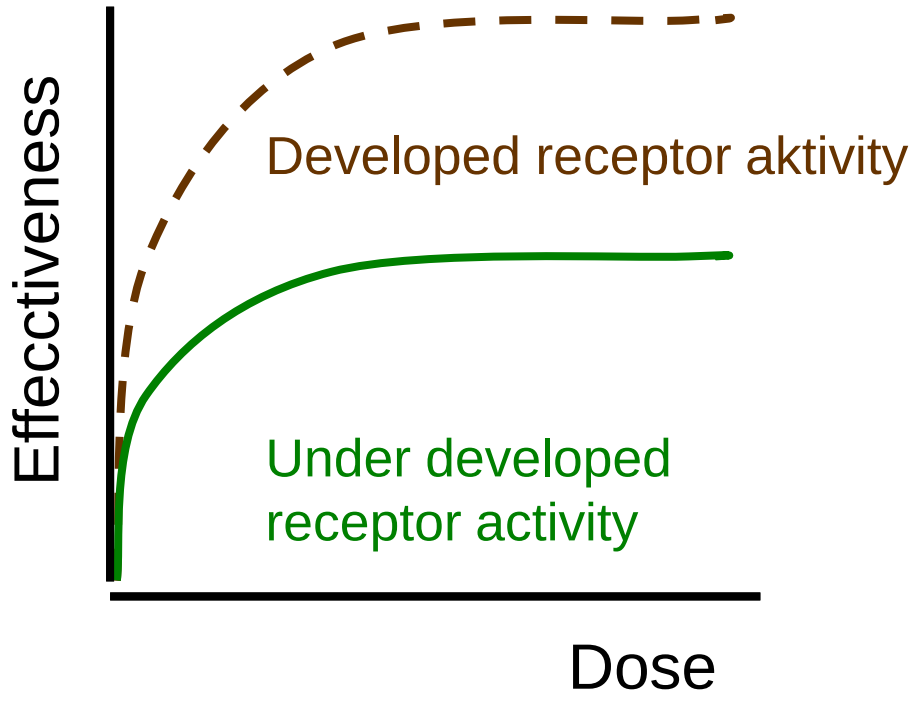
Activities of physiological functions ***decrease*** to various extent at various times

The changes of drug metabolism and effectiveness in case of under developed enzyme and/or receptor activities

Drug concentration in the plasma

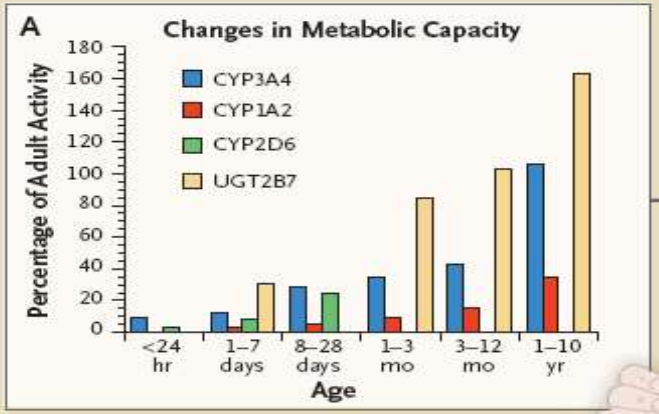


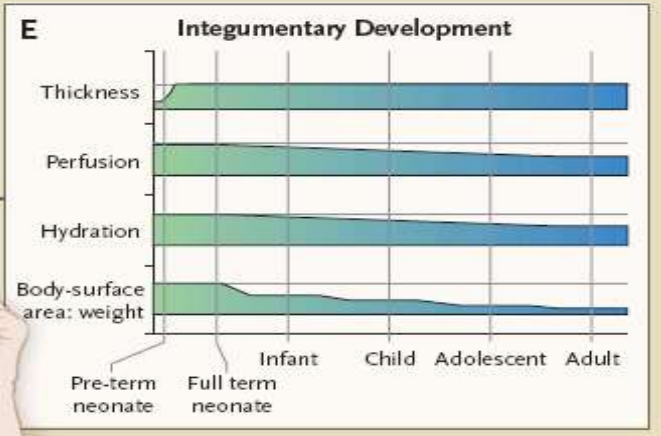
Drug effect

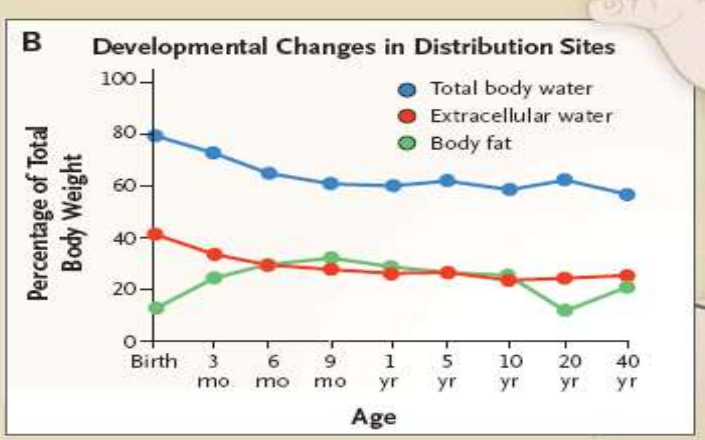


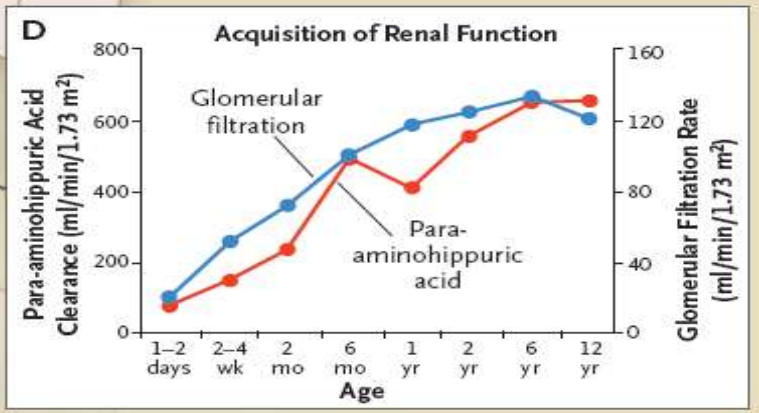
The changes of drug metabolism and effectiveness in case of under developed enzyme and/or receptor activities

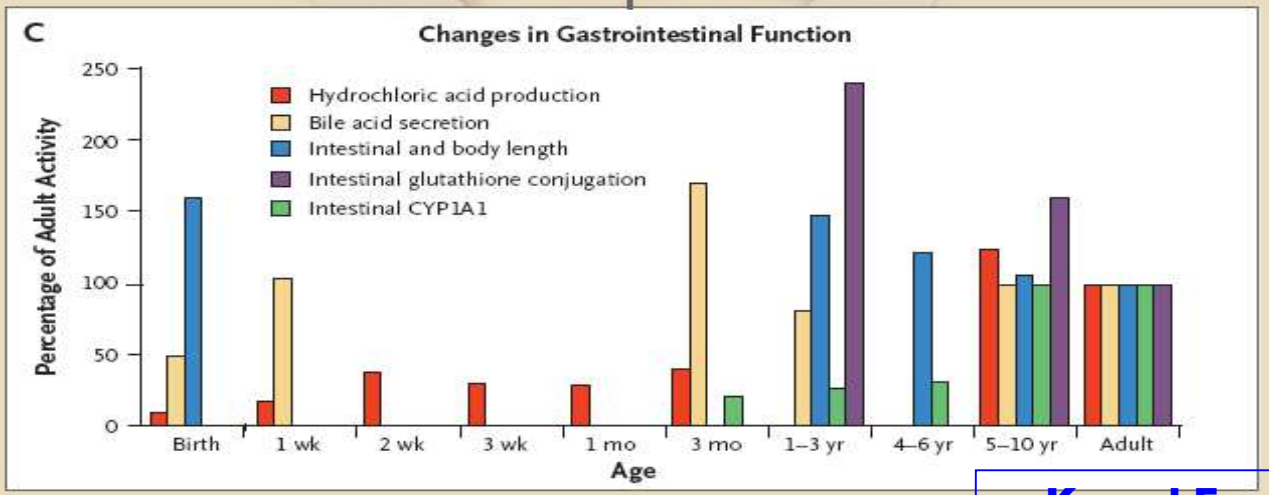
	Developed metabolism and excretion	Under developed metabolism, excretion
Developed receptor activity	Plasma level and drug effectiveness similar to normal adults	Plasma level higher than in normal adults (toxic level!) Drug effectiveness similar to normal adults
Under developed receptor activity	Plasma level similar to normal adults Drug effectiveness less than in normal adults	Plasma level higher than in normal adults (toxic level!) Drug effectiveness less than in normal adults


A
Changes in Metabolic Capacity
Percentage of Adult Activity
CYP3A4
CYP1A2
CYP2D6
UGT2B7
<24 hr
1–7 days
8–28 days
1–3 mo
3–12 mo
1–10 yr
Age


E
Integumentary Development
Thickness
Perfusion
Hydration
Body-surface area: weight
Pre-term neonate
Full term neonate
Infant
Child
Adolescent
Adult


B
Developmental Changes in Distribution Sites
Percentage of Total Body Weight
Total body water
Extracellular water
Body fat
Birth
3 mo
6 mo
9 mo
1 yr
5 yr
10 yr
20 yr
40 yr
Age


D
Acquisition of Renal Function
Para-aminohippuric Acid Clearance (ml/min/1.73 m²)
Glomerular Filtration Rate (ml/min/1.73 m²)
Glomerular filtration
Para-aminohippuric acid
1–2 days
2–4 wk
2 mo
6 mo
1 yr
2 yr
6 yr
12 yr
Age


C
Changes in Gastrointestinal Function
Percentage of Adult Activity
Hydrochloric acid production
Bile acid secretion
Intestinal and body length
Intestinal glutathione conjugation
Intestinal CYP1A1
Birth
1 wk
2 wk
3 wk
1 mo
3 mo
1–3 yr
4–6 yr
5–10 yr
Adult
Age

NEJM

Drug application in children

Body composition rapidly changing with age

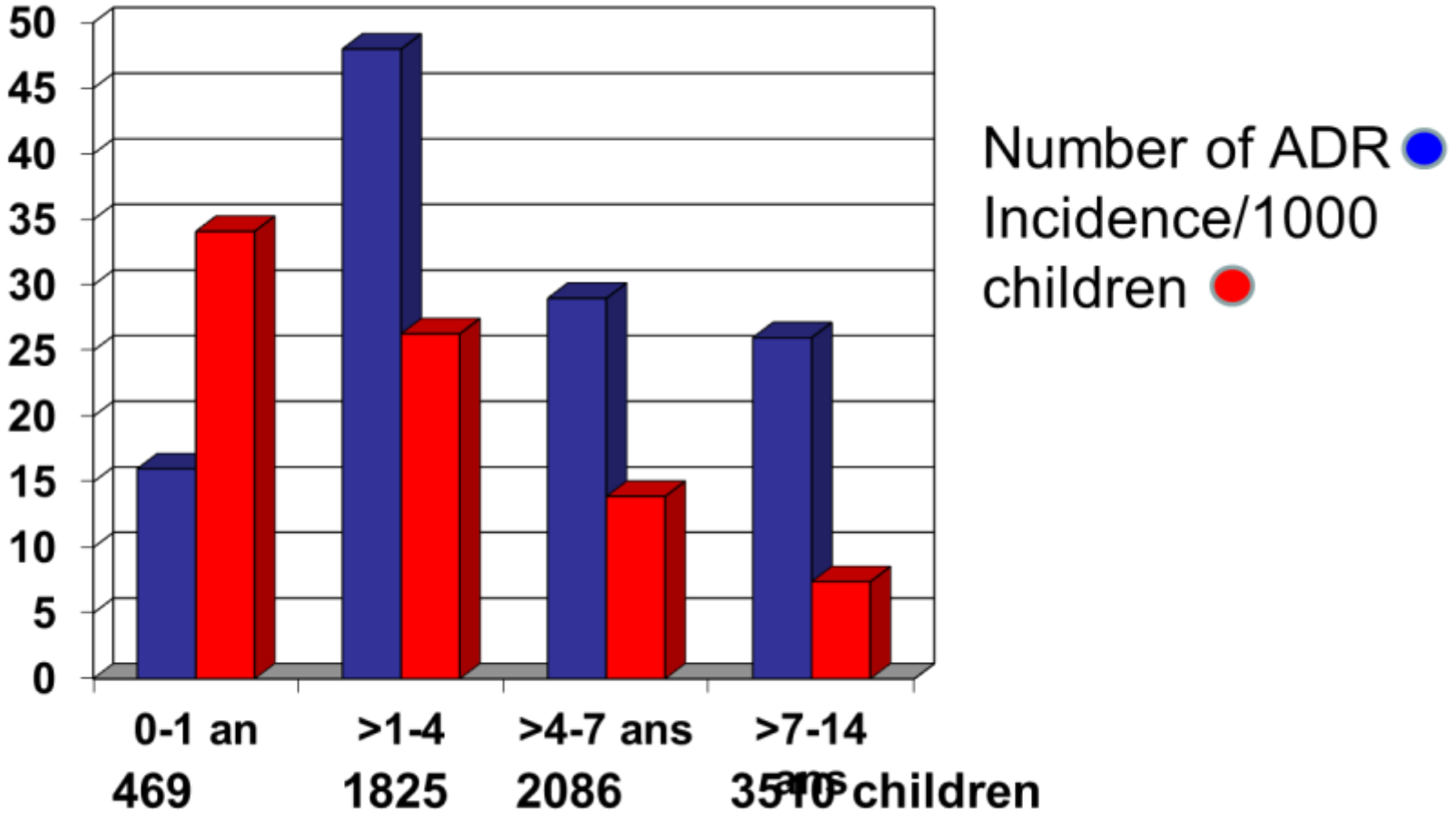
Changing pharmaco-kinetic properties

Changing pharmaco-dynamic effects

- Th recommended formulas for calculating drug dose in children give only an approximation because they cannot take into consideration the processes of maturing.
  - The results are doses below or over the optimal
- ***The doses in the various age groups must be determined by pharmacokinetic measurements and clionical dose titration***

Paediatric Network: Number of side effects in children

Menniti-Ippolito, Lancet 2000, vol 355, 1613-14



Senectas ipse morbus

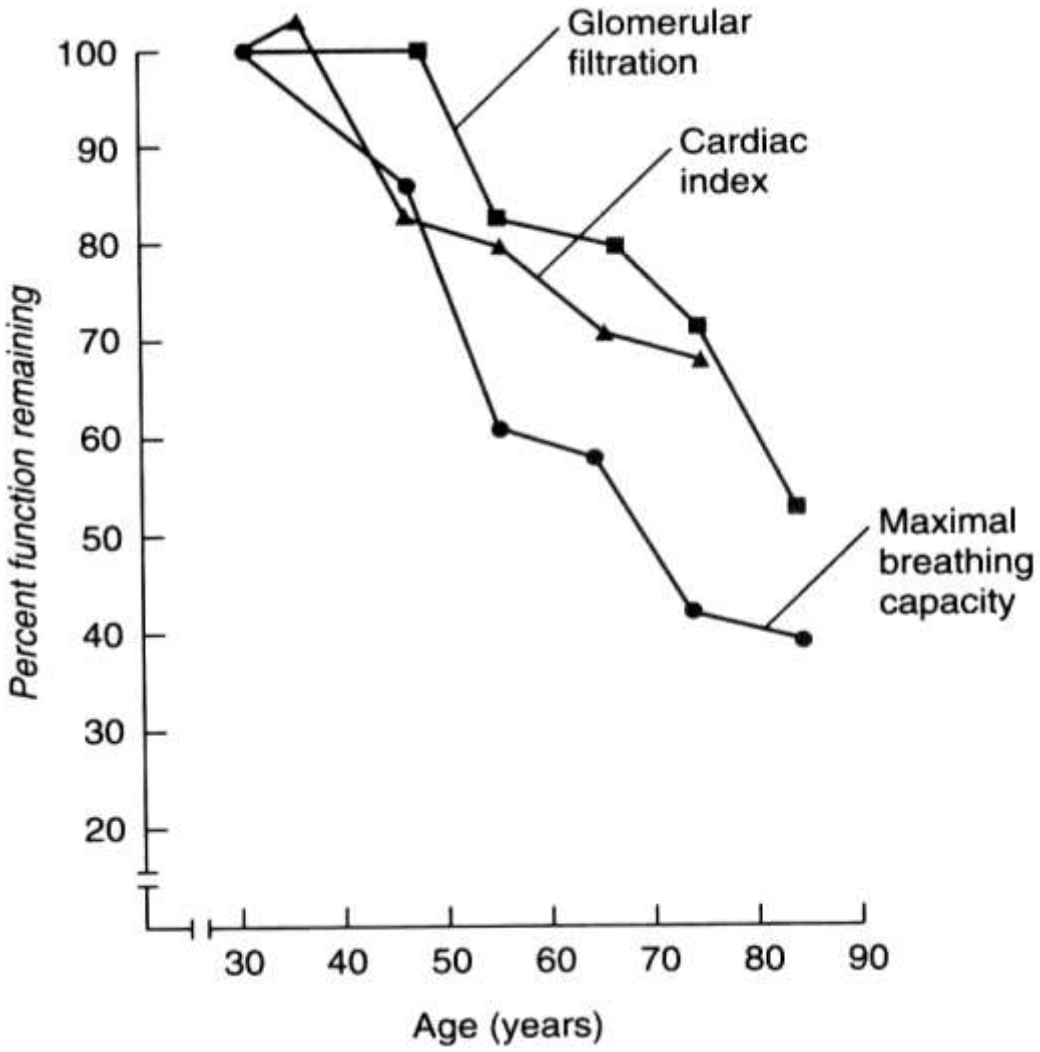
“Every man desires to live long; but no man would be old”

(Jonathan Swift, 1667–1745)

Changes of physiological functions during the life

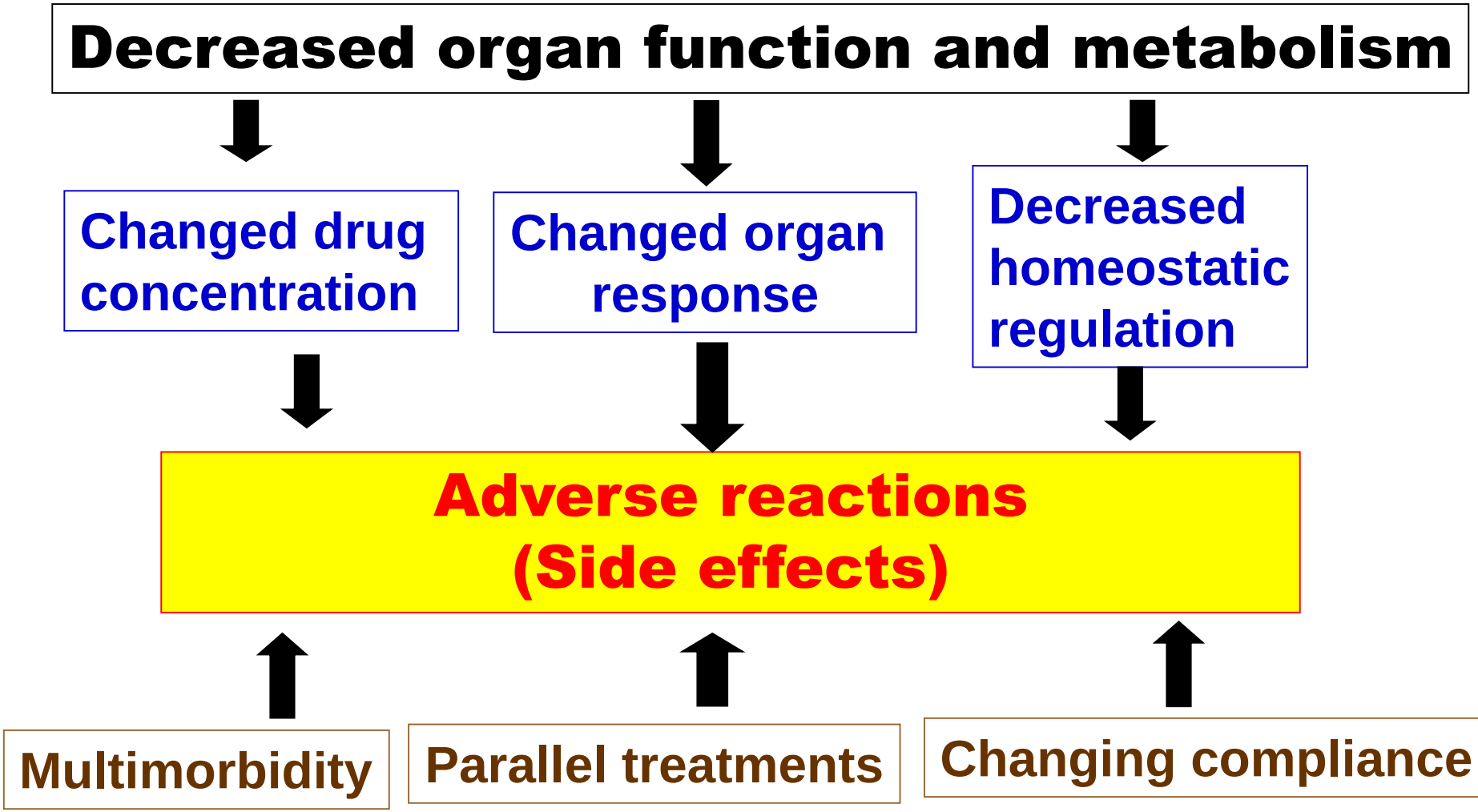
Kohn RR. Principles of Mammalian Aging. Prentice-Hall, 1978.

- The capacity of physiological functions decreases with age
- These changes might be amplified with pathologic alterations
- These changes effect pharmacokinetic behaviour of drugs



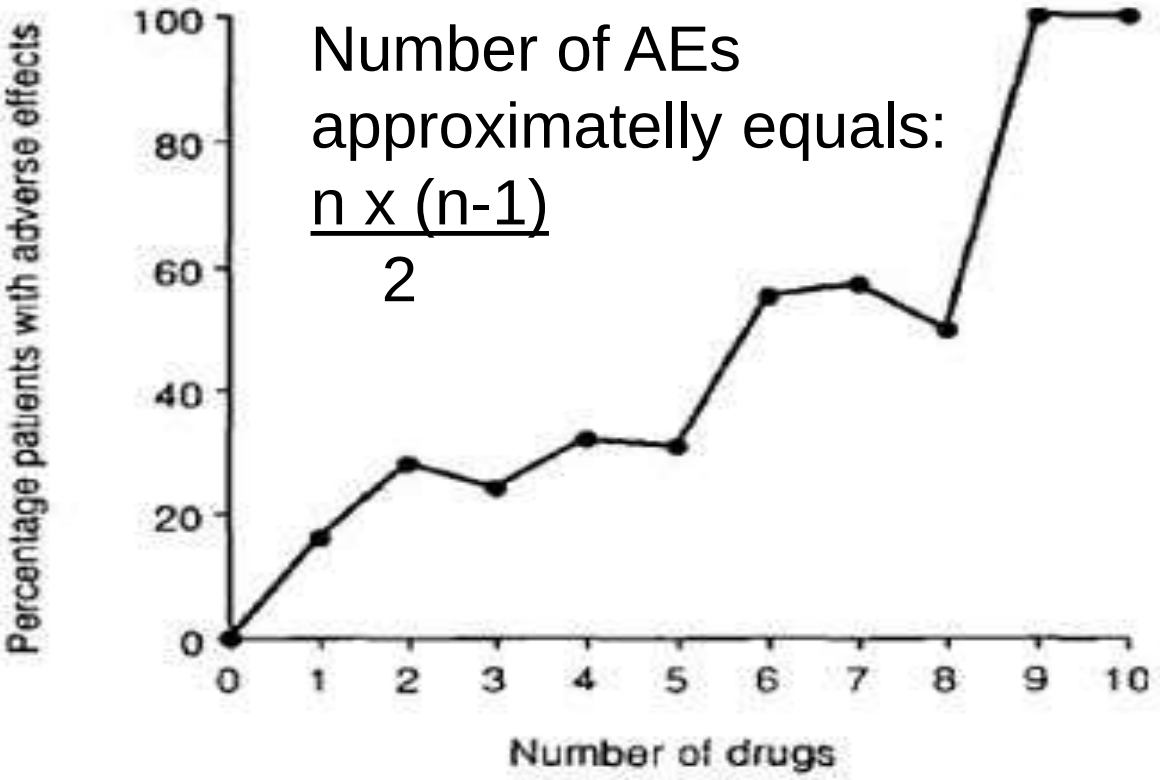
Causes leading to adverse reactions in the elderly

Wehling M és Peiter A Internist, 44:1003-1009, 2003



The relation of the number drugs and the occurrence of adverse effects

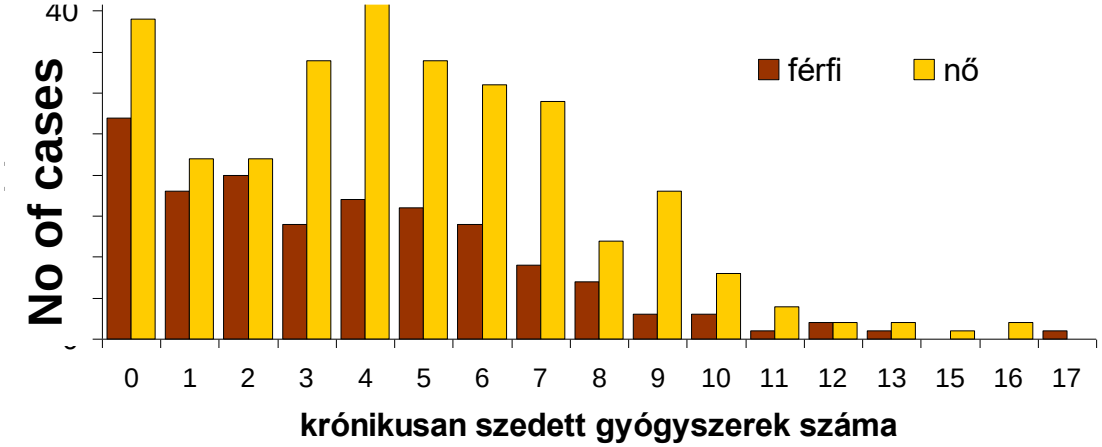
Cresswell et al. Br Med Bull. 83:259-274, 2007



- Patients > 65 years use usually ≥ 5 drugs/day simultaneously
- 1/3 of elderly hospitalisation is due to AE

Number of chronically consumed drugs in elderly patients living in a community

Soós Gy. and coworkers



males	females
73.3 yrs	74 yrs

Small community with 3000 inhabitants
Mean age of of the elderly > 65 yrs

No of drugs

	Males	Females	Total
No drugs [Cases] (%)	27 (18%)	39 (13%)	66 (15%)
< 5 drugs	69 (45%)	120 (40%)	189 (41%)
≥ 5 drugs	57 (37%)	143 (47%)	200 (44%)
Total	*153(100%)*	*302 (100%)*	*455(100%)*

Mark Howard **Beers** MD
1955-2009

Beers List

Courtesy of Gy. Soós

The Beers Criteria is a list of specific medications that are generally considered inappropriate when given to elderly people

Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Beers MH et al. Arch Intern Med. 1991 Sep;151(9):1825-32.

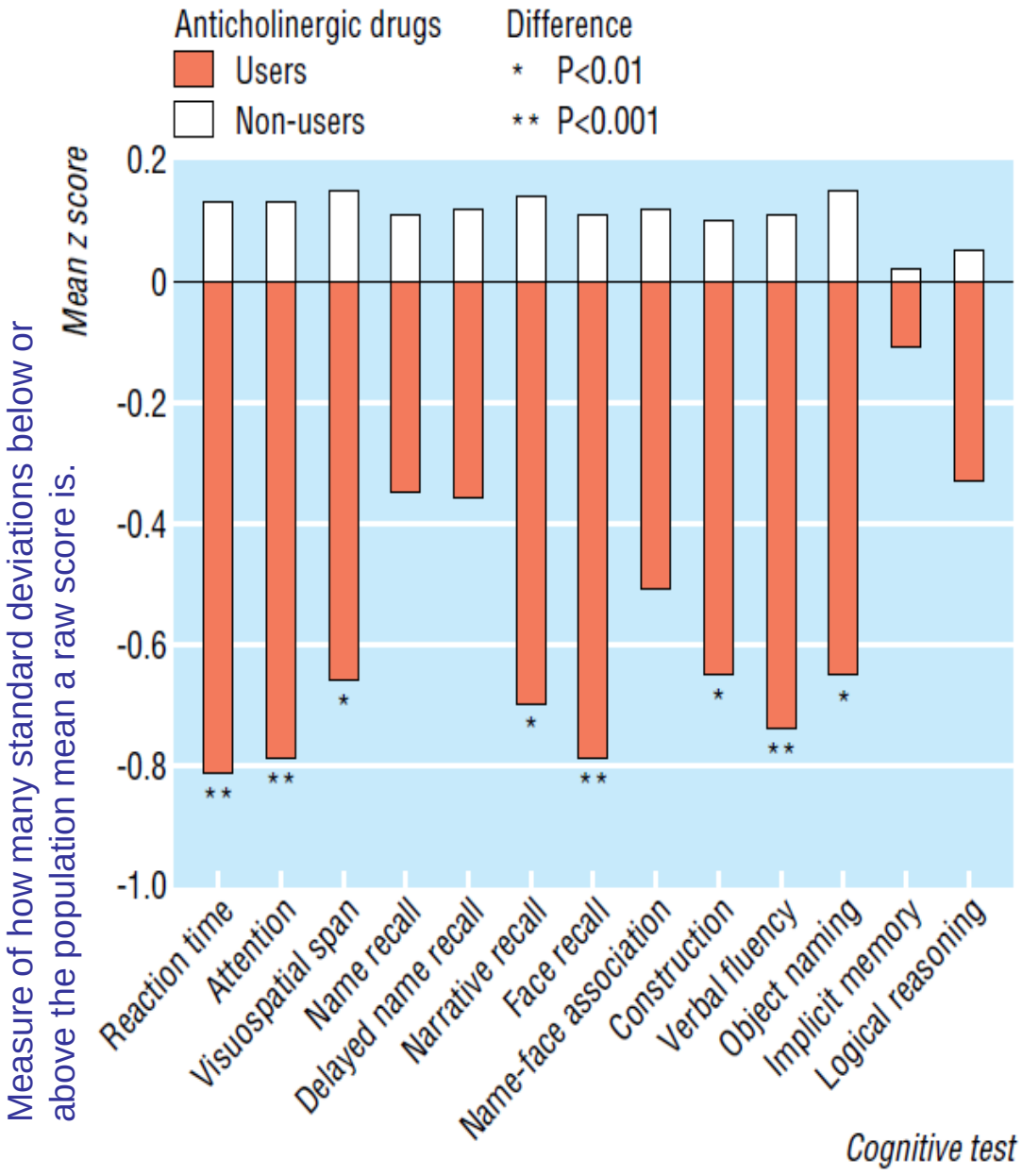
Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults
Fick DM et al. Arch Intern Med. 2003;163:2716-2724.

Association of severe side effects frequently occurring in elderly patients with drugs

Signs and symptoms	Groups of medicines
Anticholinergic side effects (delirium)	Antiemetics, drugs affecting Parkinson-disease, spasmolytics, analgetics, antiarrhythmics, antihistamines, tricyclic antidepressants, sedatives (neuroleptics)
Confusion	Morphine and derivatives, benzodiazepines, antidepressants, classical antipsychotic drugs (neuroleptics), drugs affecting Parkinson-disease, anticholinergic agents, centrally acting antihypertensive agents, corticosteroids > 40 mg daily dose

Effect of anticholinergic drugs on cognitive functions

Ancelin ML et al. BMJ, 2006 doi 10.1136/bmj.38740.439664.DE



Mild cognitive impairment

- 297 pts not using anticholinergic agents 35% (95% CI 30%-41%)
- 30 pts using regularly anticholinergic agents 80% (95%CI 66%-94%)
- Predictive factors: use of anticholinergic drugs: Odds ratio: 5.12 (p<0.001; age 1.09 (p>0.001)

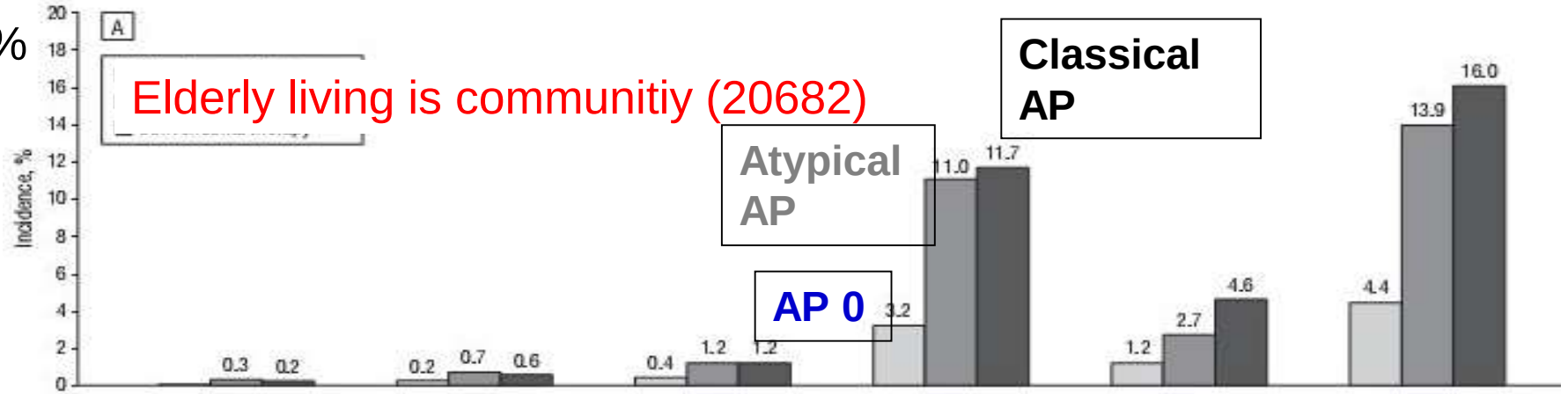
Association of severe side effects of drugs frequently occurring in elderly patients

Groups of medicines	Increased risk of falls due to various effects of drugs
Benzodiazepines Tricyclic antidepressants	Sedation, confusion, equilibrium disturbance
Antihypertensive agents	Hypotension
Antipsychotics, antidepressants	Parkinson syndrome, bradykinesia, rigor, tremor
Insulin and oral antidiabetics	Hypoglycaemia
Aminoglycoside antibiotics, acetylsalicylic acid, chinidine	Vestibular impairment

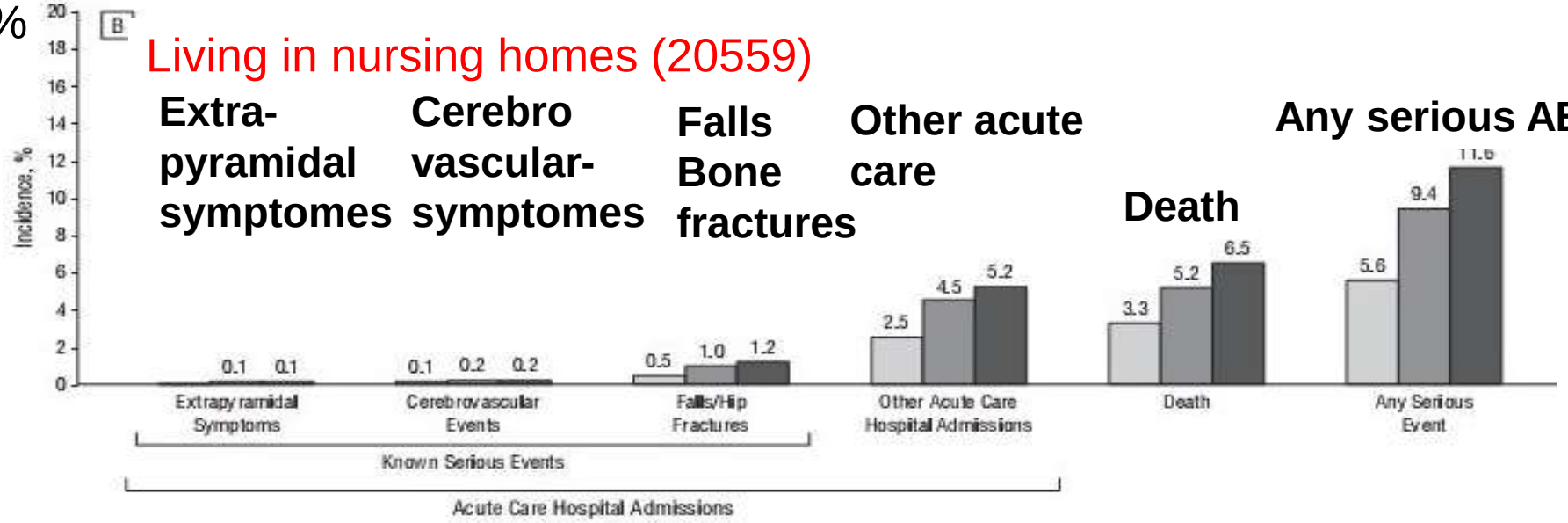
The serious side effects of antipsychotic therapy in elderly patients

Rochon et al., Arch Intern Med, 168:1090-1096, 2008

20%



20%



Acute hospitalization

Background and golden rules of geriatric drug therapy

Body composition changing with age

Changing pharmacokinetic properities

- Start low

Changing pharmacodynamic effects

- Go slow
- Slow titration untill the optimal dose is reached

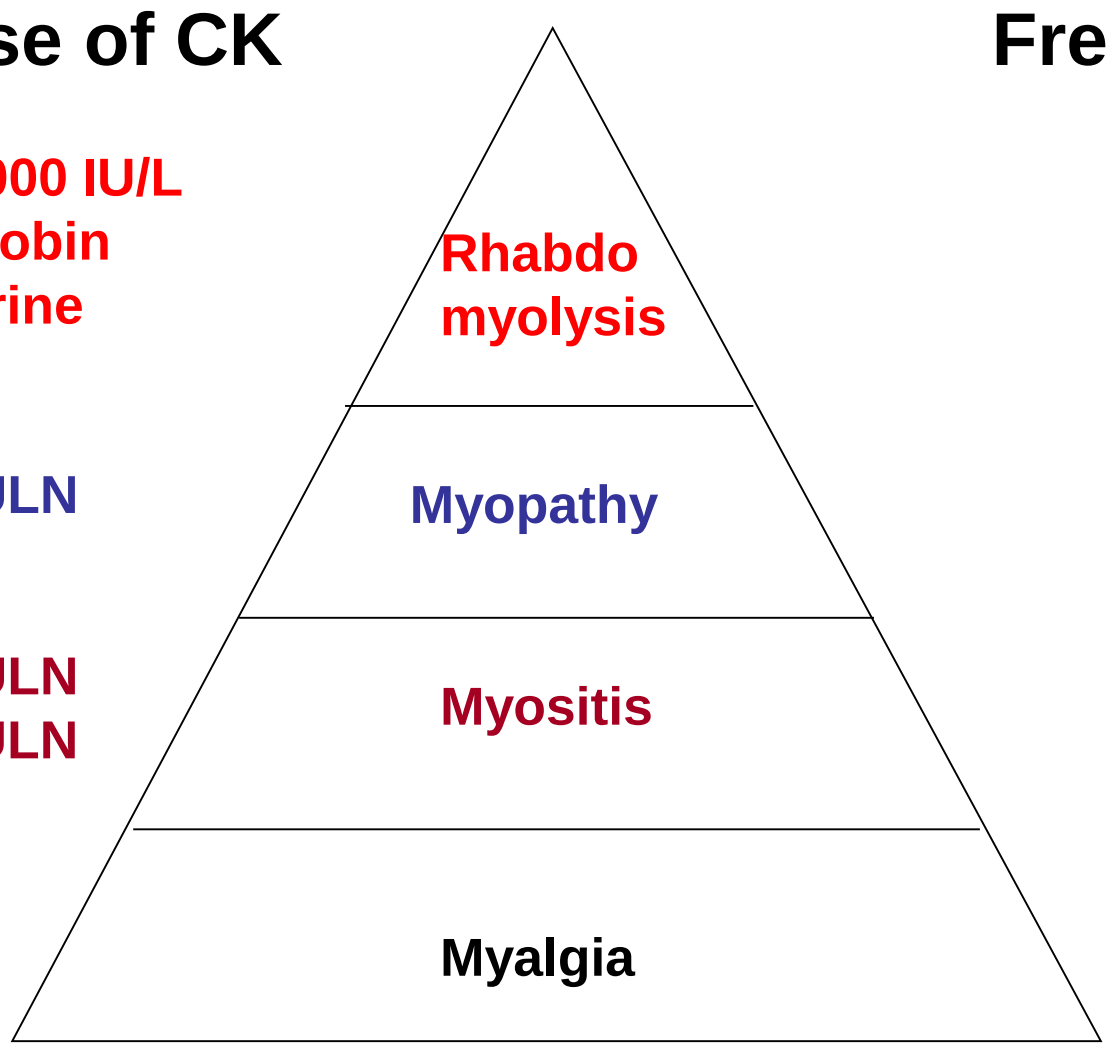
Careful observation and follow-up

Kerpel-Fronius S.:

Some examples

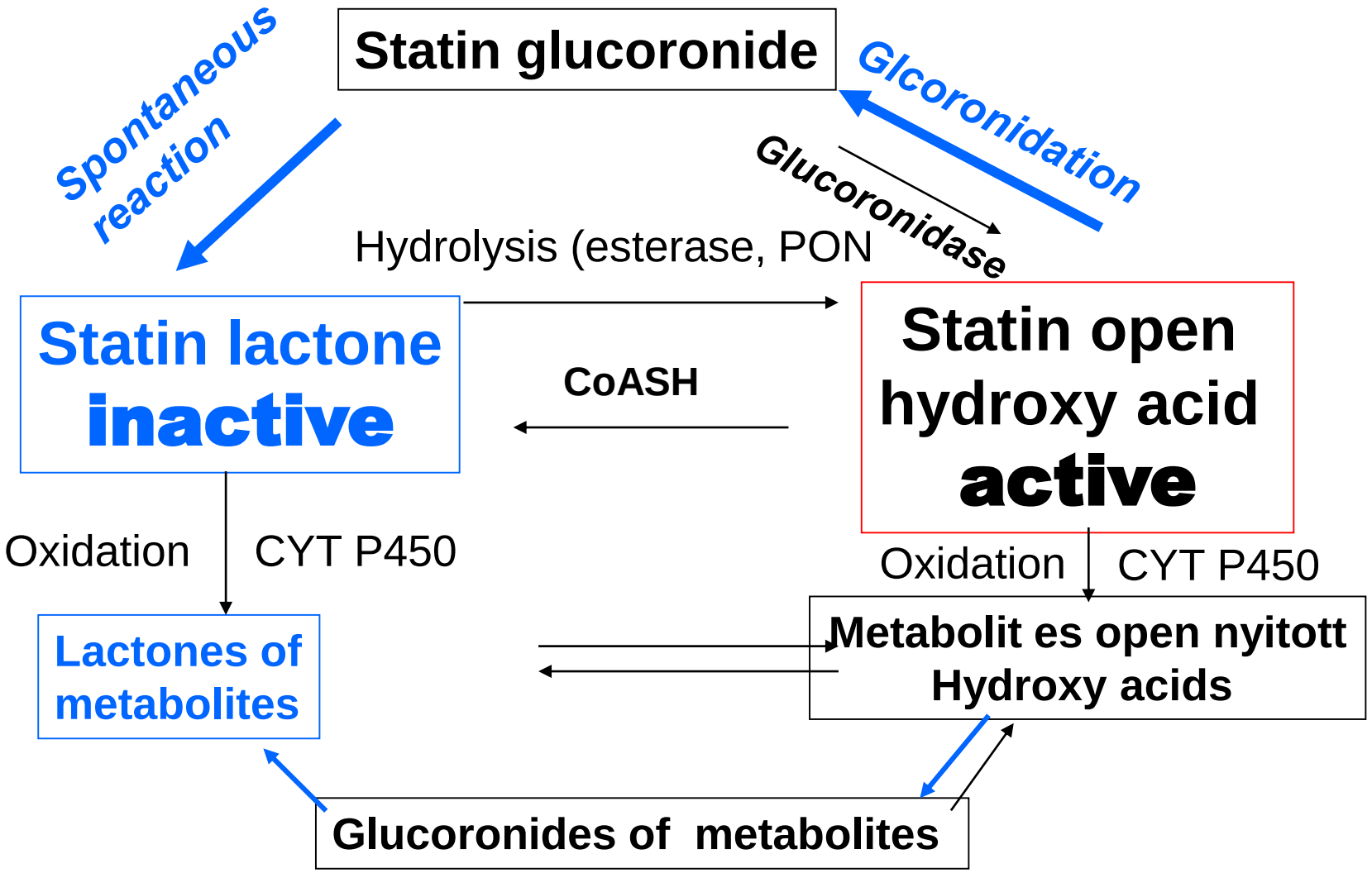
Small molecular weight chemical medicinal products

Muscle damage during statin treatment



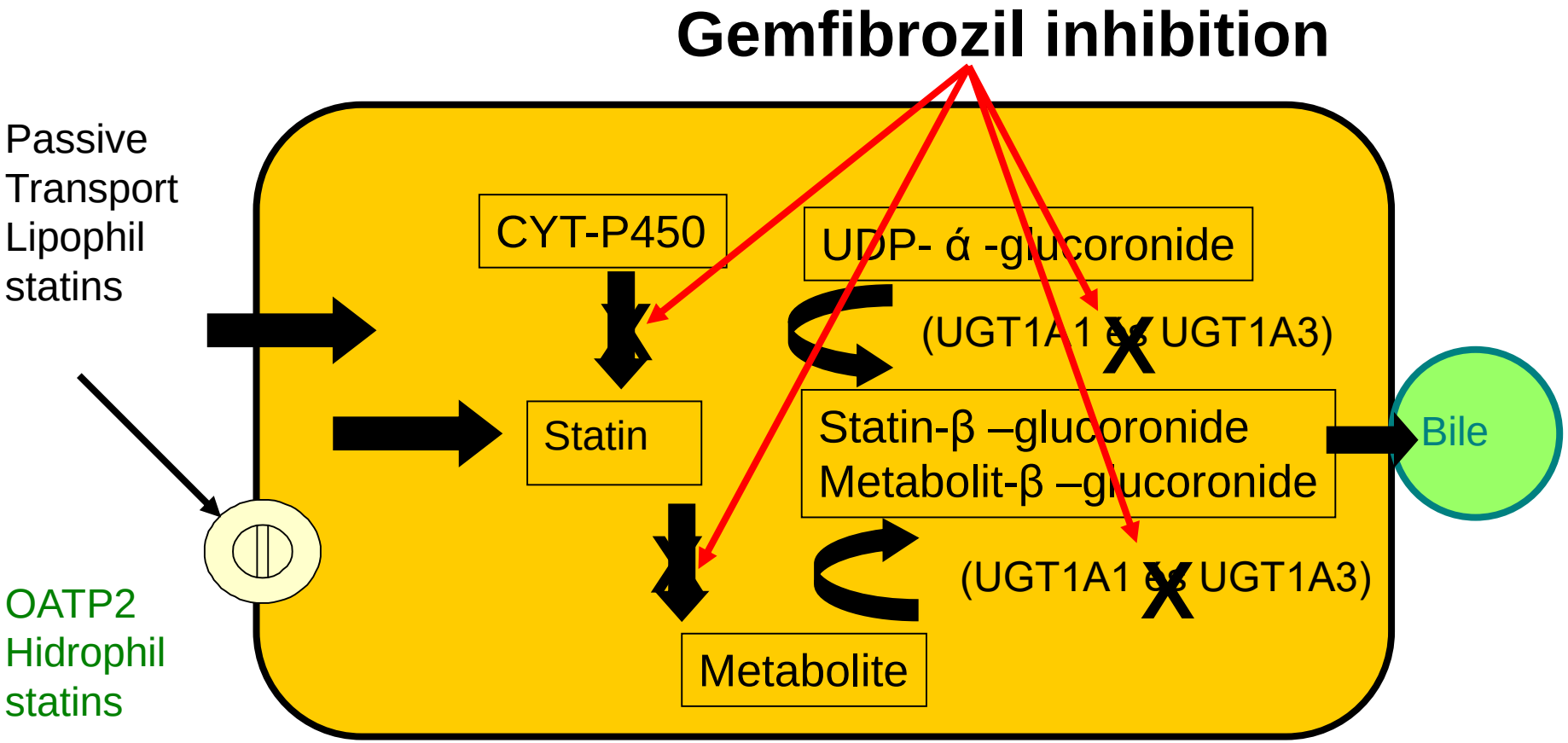
The metabolism and inactivation of statins

Prueksaritanont et al. Drug Metab Disspos. 30:505. 2002.



The metabolic background of the cerivastatin tragedy

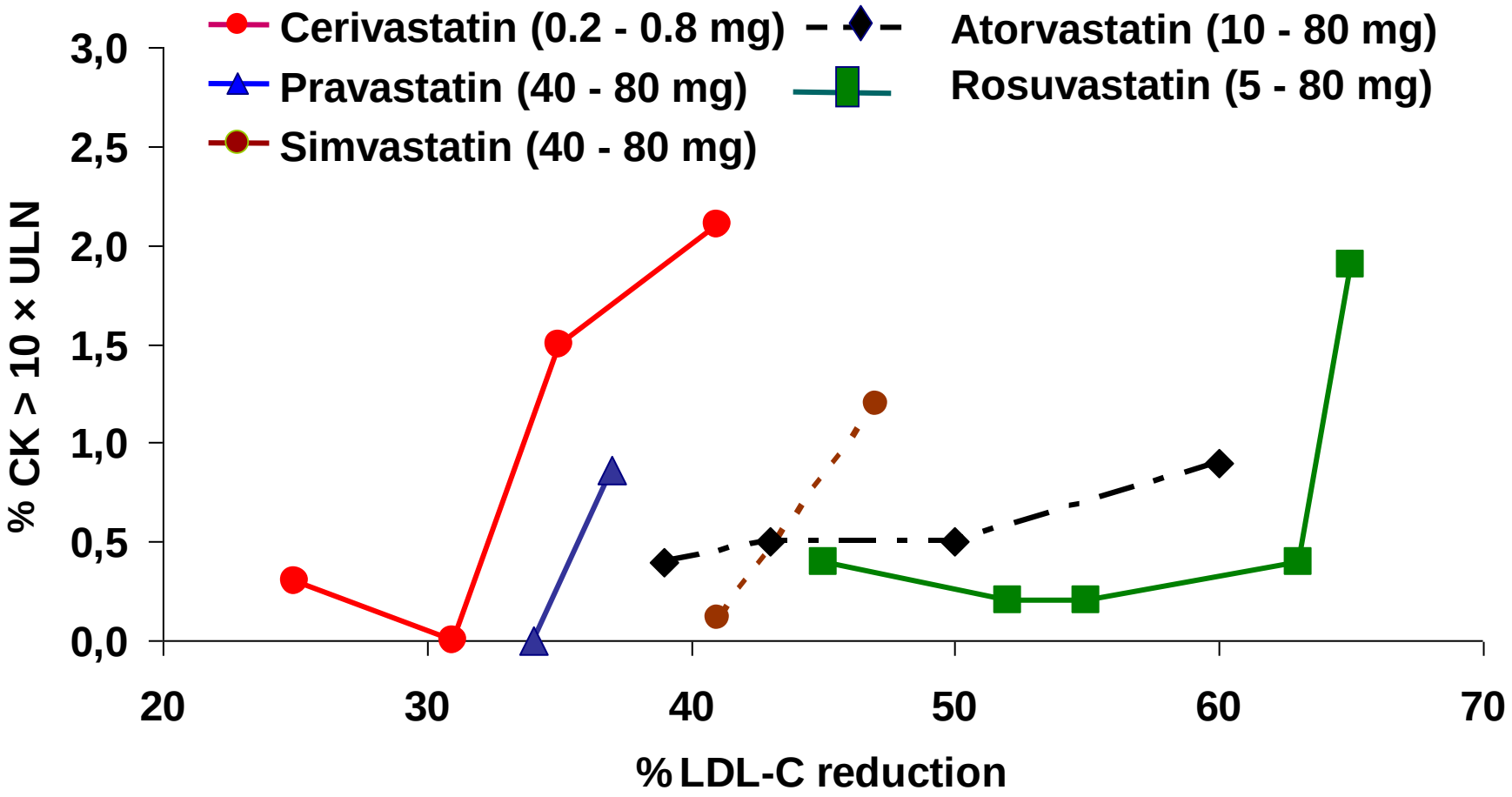
Ballantine CM et al. Arch Intern Med 163:553. 2003



UDP-glcoronide-transferase (UGT1A1, UGT1A3)
Organic Acid Transporter Polypeptide (OATP)

Frequency of myositis (CK > 10 × ULN) related to % LDL-C Reduction

Brewer HB. Am J Cardiol. 92:22K. 2003.



Reported cases with rhabdomyolysis (FDA)

Chang JT et al. Pharmacoepidem Drug Safety. 13:417. 2004

Drug	Atorva statin	Ceriva statin	Fluva statin	Lova statin	Prava statin	Simva statin
Monotherapy	45	200	1	120	17	99
No of pres-criptions (000)	147610	11038	37791	97336	82000	118986
Reporting rate /100000 presc	0.03	1.81	0.0	0.12	0.02	0.08
+ Gemfibrozil No of cases	*6*	*279*	*0*	*60*	*2*	*37*
No of pres-criptions (000)	*1198*	*22*	*316*	*2109*	*1422*	*962*
Reporting rate /100000 presc	*0.50*	*1248.7*	*0.0*	*2.84*	*0.14*	*3.85*

The safety of the patients is the joint responsibility of the pharmaceutical industry, drug regulatory agency, medical doctors, pharmacists and finally of the patients themselves