# Vedecké dôkazy o bezpečnosti a účinnosti biosimilárov v onkológii

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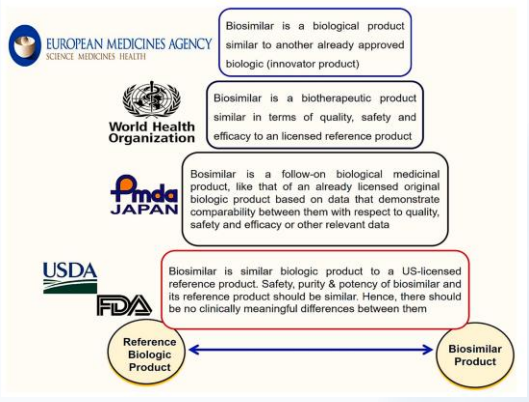
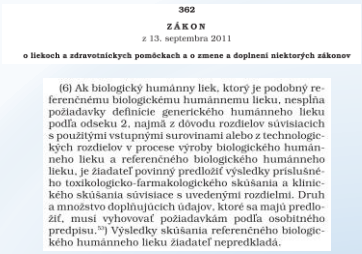
**Biosimilars (biosimilárne lieky, biosimiláry)**
- komplexná oblasť
- neexistuje jedna presná definícia (EMA, WHO, FDA,...)



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ZÁKON

z 13. septembra 2011

o liekoch a zdravotníckych pomôckach a o zmene a doplnení niektorých zákonov

(6) Ak biologický humánny liek, ktorý je podobný referenčnému biologickému humánnemu lieku, nespĺňa požiadavky definície generického humánneho lieku podľa odseku 2, najmä z dôvodu rozdielov súvisiacich s použitými vstupnými surovinami alebo z technologických rozdielov v procese výroby biologického humánneho lieku a referenčného biologického humánneho lieku, je žiadateľ povinný predložiť výsledky príslušného toxikologicko-farmakologického skúšania a klinického skúšania súvisiace s uvedenými rozdielmi. Druh a množstvo doplňujúcich údajov, ktoré sa majú predložiť, musí vyhovovať požiadavkám podľa osobitného predpisu.[20]) Výsledky skúšania referenčného biologického humánneho lieku žiadateľ nepredkladá.

Oficiálne definície biologicky podobných liekov od rôznych regulačných agentúr.

## Biosimilars (biosimilárne lieky, biosimiláry)

- Prvá definícia konceptu biosimilárov v Európskej legislatíve – **2003**
- Implementácia konceptu – **2005** – *Regulatory guidelines EMA*
- Prvý biosimilár v EU – **2006**

– Omnitrope® (*biosimilar recombinant human growth hormone [**rhGH**]; Sandoz, Kundl, Austria*)

- Prvý biosimilár v USA – **2015**

– Zarxio® (*biosimilar [**filgrastim**]; Sandoz Inc.*)

**Filgrastim-Pegfilgrastim** – Ľudský G-CSF (faktor stimulujúci kolónie granulocytov) produkovaný technológiou rekombinantnej DNA; liečba neutropénie, mobilizácia progenitorových buniek v periférnej krvi

**Epoetín alfa** - Liečba symptomatickej anémie indukovanej chemoterapiou u pacientov s malígnym nádorovým ochorením

**Interferón alfa** – Mnohopočetný myelóm, Folikulárny lymfóm, Karcinoidný nádor, Malígny melanóm, Leukémie, *Chronická hepatitída B a C*

**Rituximab** – anti-CD20 MAb; Non-Hodgkinov lymfóm, folikulový (NHL), Chronická lymfocytová leukémia (CLL), *Reumatoidná artritída, Granulomatóza s polyangiitídou a mikroskopická polyangiitída, Pemphigus vulgaris*

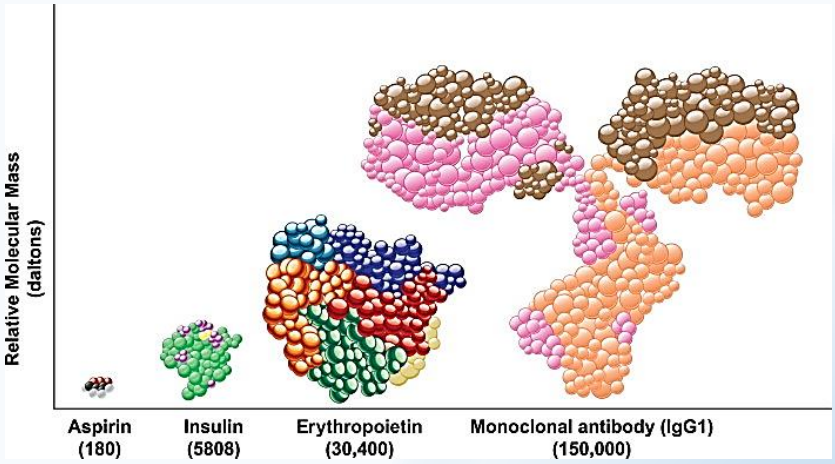
**Trastuzumab** – anti-HER2 Mab (receptor 2 ľudského epidermálneho rastového faktora); Včasný a metastatický karcinóm prsníka a metastatický karcinóm žalúdka

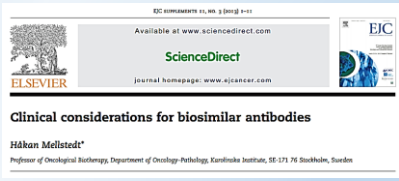
**Bevacizumab** – anti-VEGF MAb (vaskulárny endotelový rastový faktor); Metastatický karcinóm hrubého čreva alebo konečníka, Metastatický karcinóm prsníka, Neskvamózny nemalobunkový karcinóm pľúc, Pokročilý a/alebo metastatický karcinóm obličkových buniek, Epiteliálny karcinóm vaječníkov, karcinóm Fallopiovej trubice a primárny peritoneálny karcinóm, Karcinóm krčka maternice


Table 1. Bevacizumab, rituximab and trastuzumab: type of monoclonal antibody, indications, European Medicine Agency authorization date and patent expiry date in the European Union.

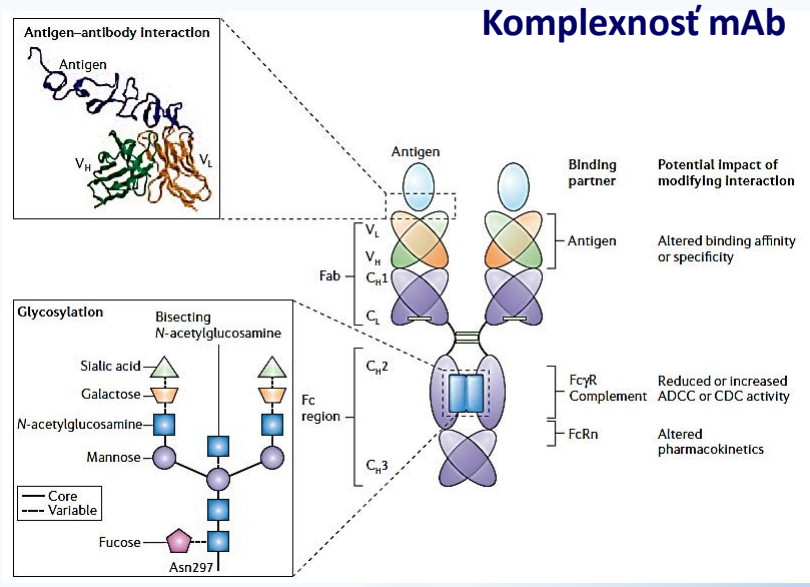
| | Rituximab | Trastuzumab | Bevacizumab |
|---|---|---|---|
| Type of mAb | Chimeric IgG1 | Humanized IgG1 | Humanized IgG1 |
| Antigen | CD20 in B cells | HER2 | VEGF |
| Indications | B-cell NHL: FL, DLBCL CLL<br>RA granulomatosis with polyangiitis, microscopic polyangiitis pemphigus vulgaris | EBC<br>MBC<br>Metastatic gastric cancer | Metastatic carcinoma of colon or rectum,<br>MBC<br>NSCLC<br>Metastatic renal cell cancer, metastatic carcinoma of cervix, epithelial ovarian, fallopian tube or primary peritoneal cancer |
| Trade name (manufacturer) | MabThera® /Rituxan® (Roche) | Herceptin® (Genentech) | Avastin® (Genentech) |
| EMA authorization date | 1998 | 2000 | 2005 |
| Patent expiry date in EU | 2013 | 2014 | 2020† |

Chimeric mAb typically comprise variable regions derived from a murine source and constant regions (65%) derived from a human source [13]. Humanized mAb are predominantly (90%) engineered from a human source [13].
†Some patents related to bevacizumab expire later in EU [14].
CLL: Chronic lymphocytic leukaemia; DLBCL: Diffuse large B cell lymphoma; EBC: Early breast cancer; EMA: European Medicine Agency; EU: Europe; FL: Follicular lymphoma; mAb: Monoclonal antibody; MBC: Metastatic breast cancer; NHL: Non-Hodgkin lymphomas; NSCLC: Non-small-cell lung cancer; RA: Rheumatoid arthritis.




## Komplexnosť mAb




ADCC - antibody-dependent cell-mediated cytotoxicity
CDC - complement dependent cytotoxicity

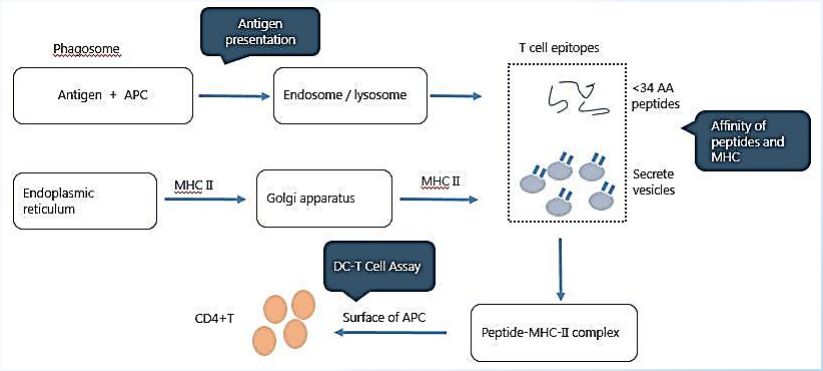
Carter PJ: Nat Rev Immunol. 2006 May;6(5):343-57.

# Imunogenicita

Imunitná odpoveď na liečivo

- (Terapeutická – vakcinácia)
- NÚ - biologické lieky (všetky)

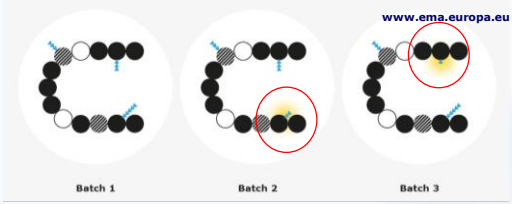
(viacero príkladov: neutralizácia nielen liečiva ale aj endogénneho proteínu – MAb proti exogénnemu Epo neutralizuje aj endogénny Epo = aplázia erytropoézy)



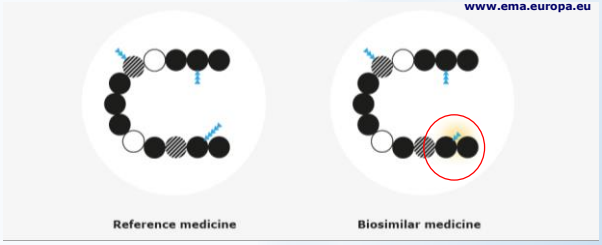

Zlyhanie jedného biologika ešte nevylučuje úspešné použitie iného

Biologické lieky – obsahujú aktívne látky pochádzajúce z biologických zdrojov ako žijúce bunky alebo organizmy (prakticky nemožné dosiahnuť identické kópie veľkých molekúl)

Prípustná variabilita medzi šaržami biologického lieku




Prípustná variabilita medzi referenčným (originálnym) liekom a biosimilars




Dostatok dôkazov, že takéto malé rozdiely nemajú vplyv na kvalitu, bezpečnosť a účinnosť

## Vývoj inovatívneho vs. biosimilárneho lieku

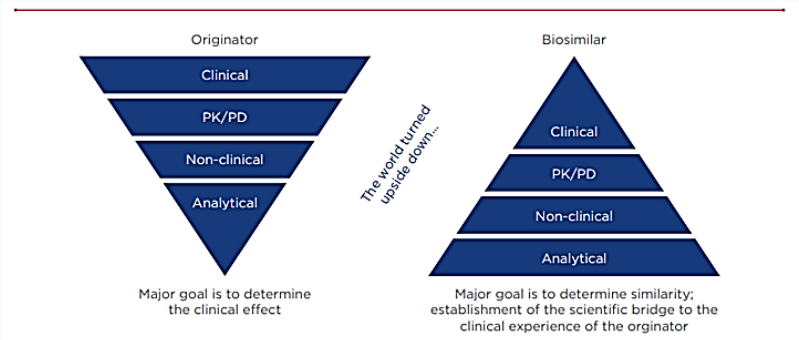
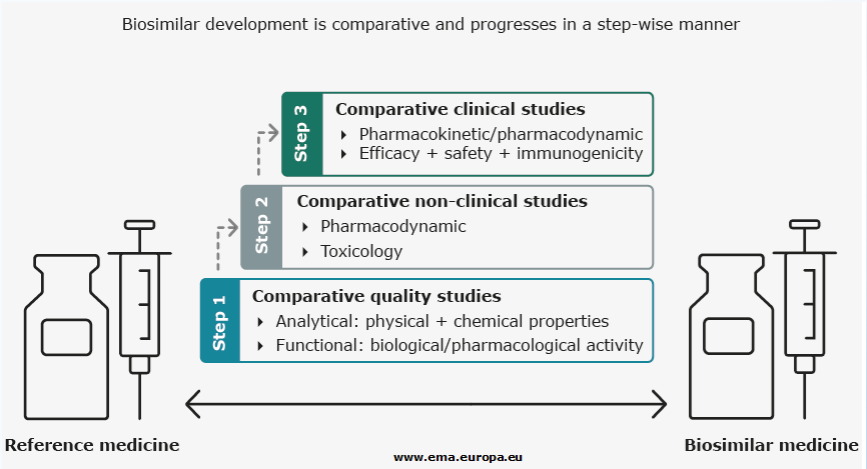



**Figure 2: Comparison of the development approach for originator biologicals and biosimilars.**
PD: pharmacodynamics; PK: pharmacokinetics.

López-Guillermo A, et al. EMJ Hematol. 2016;4[1]:30-37

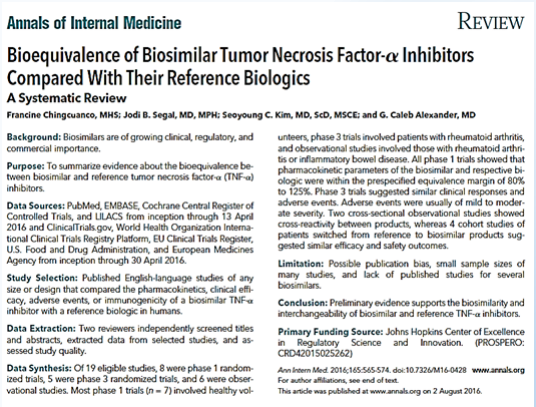
**Komparatívne štúdie** – 1.+2. in vitro modely, 1.-cieľom je porovnať štruktúru a biologickú funkciu, 2.-cieľom je porovnať väzbu a aktiváciu (resp. inhibíciu) fyziologického cieľa a fyziologický účinok, 3.-cieľom nie je dokumentovať účinnosť a bezpečnosť, ale potvrdiť biologickú podobnosť



## Klinické skúšky pre biosimilars

**Nemusia dokázať účinnosť a bezpečnosť** u človeka ako v prípade ref.lieku
Musia vylúčiť klinicky významné rozdiely medzi biosimilars a ref.liekom a potvrdiť biosimilaritu

Kľúčové aspekty:
Vylúčiť odlišnosti, ktoré môžu ovplyvniť farmakokinetiku, účinnosť, bezpečnosť, imunogenicitu



Annals of Internal Medicine — REVIEW

**Bioequivalence of Biosimilar Tumor Necrosis Factor-α Inhibitors Compared With Their Reference Biologics**

**A Systematic Review**

Francine Chingcuanco, MHS; Jodi B. Segal, MD, MPH; Seoyoung C. Kim, MD, ScD, MSCE; and G. Caleb Alexander, MD

**Background:** Biosimilars are of growing clinical, regulatory, and commercial importance.

**Purpose:** To summarize evidence about the bioequivalence between biosimilar and reference tumor necrosis factor-α (TNF-α) inhibitors.

**Data Sources:** PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and LILACS from inception through 13 April 2016 and ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, EU Clinical Trials Register, U.S. Food and Drug Administration, and European Medicines Agency from inception through 30 April 2016.

**Study Selection:** Published English-language studies of any size or design that compared the pharmacokinetics, clinical efficacy, adverse events, or immunogenicity of a biosimilar TNF-α inhibitor with a reference biologic in humans.

**Data Extraction:** Two reviewers independently screened titles and abstracts, extracted data from selected studies, and assessed study quality.

**Data Synthesis:** Of 19 eligible studies, 8 were phase 1 randomized trials, 5 were phase 3 randomized trials, and 6 were observational studies. Most phase 1 trials ($n = 7$) involved healthy volunteers, phase 3 trials involved patients with rheumatoid arthritis, and observational studies involved those with rheumatoid arthritis or inflammatory bowel disease. All phase 1 trials showed that pharmacokinetic parameters of the biosimilar and respective biologic were within the prespecified equivalence margin of 80% to 125%. Phase 3 trials suggested similar clinical responses and adverse events. Adverse events were usually of mild to moderate severity. Two cross-sectional observational studies showed cross-reactivity between products, whereas 4 cohort studies of patients switched from reference to biosimilar products suggested similar efficacy and safety outcomes.

**Limitation:** Possible publication bias, small sample sizes of many studies, and lack of published studies for several biosimilars.

**Conclusion:** Preliminary evidence supports the biosimilarity and interchangeability of biosimilar and reference TNF-α inhibitors.

**Primary Funding Source:** Johns Hopkins Center of Excellence in Regulatory Science and Innovation. (PROSPERO: CRD42015025262)

*Ann Intern Med.* 2016;165:565-574. doi:10.7326/M16-0428 www.annals.org

For author affiliations, see end of text.

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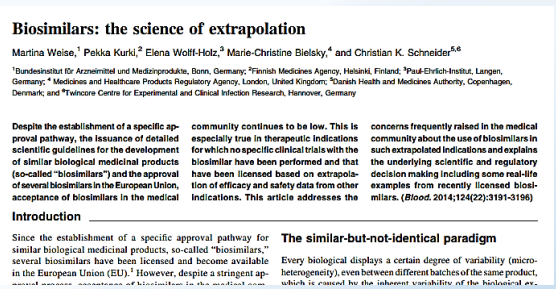
## Extrapolácia klinickej účinnosti

Ak je biosimilar veľmi podobné ref.lieku a má porovnateľnú bezpečnosť a účinnosť v jednej terapeutickej indikácii, údaje o bezpečnosti a účinnosti môžu byť extrapolované **pre iné indikácie** ref.lieku. Sú potrebné ale robustné komparatívne štúdie (kvality, predklinické, klinické).



**Biosimilars: the science of extrapolation**

Martina Weise,[1] Pekka Kurki,[2] Elena Wolff-Holz,[3] Marie-Christine Bielsky,[4] and Christian K. Schneider[5,6]

[1]Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany; [2]Finnish Medicines Agency, Helsinki, Finland; [3]Paul-Ehrlich-Institut, Langen, Germany; [4] Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; [5]Danish Health and Medicines Authority, Copenhagen, Denmark; and [6]Twincore Centre for Experimental and Clinical Infection Research, Hannover, Germany

**Despite the establishment of a specific approval pathway, the issuance of detailed scientific guidelines for the development of similar biological medicinal products (so-called "biosimilars") and the approval of several biosimilars in the European Union, acceptance of biosimilars in the medical community continues to be low. This is especially true in therapeutic indications for which no specific clinical trials with the biosimilar have been performed and that have been licensed based on extrapolation of efficacy and safety data from other indications. This article addresses the concerns frequently raised in the medical community about the use of biosimilars in such extrapolated indications and explains the underlying scientific and regulatory decision making including some real-life examples from recently licensed biosimilars. (*Blood.* 2014;124(22):3191-3196)**

**Introduction**

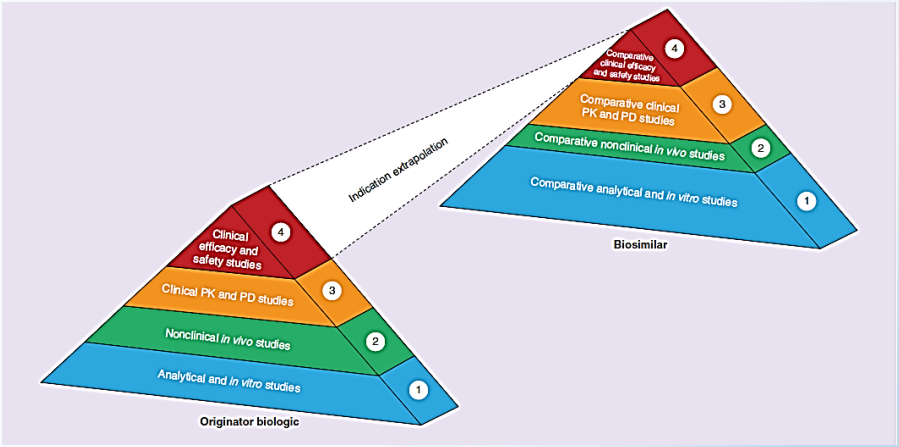
Since the establishment of a specific approval pathway for similar biological medicinal products, so-called "biosimilars," several biosimilars have been licensed and become available in the European Union (EU).[1] However, despite a stringent ap-

**The similar-but-not-identical paradigm**

Every biological displays a certain degree of variability (micro-heterogeneity), even between different batches of the same product,

Kritériá pre extrapoláciu:
Mechanizmus účinku
Relevantná populácia štúdie
Odlišnosť klinických podmienok
Extrapolácia údajov o bezpečnosti
Extrapolácia údajov o imunogenicite (rizika imunitných reakcií)

# Postavenie extrapolácie vo vývoji biosimilárov




Ogura M, et al. Future Oncol. 2017;13:45-53

# Extrapolácia

- Vzhľadom na spôsob, akým sa biologicky podobné lieky vyvíjajú, nie je vždy potrebné uskutočňovať klinické štúdie o biologicky podobnom lieku pri všetkých ochoreniach, pri ktorých sa preukázala účinnosť referenčného lieku. Namiesto toho je niekedy možné rozšíriť údaje o bezpečnosti a účinnosti zo štúdií jedného ochorenia na ostatné chorobné stavy. Tento postup je známy ako extrapolácia. Rozhodnutie o tom, či sa na liečbu ďalších stavov budú vyžadovať nové klinické štúdie, prijíma Európska agentúra pre lieky (EMA) podľa jednotlivých prípadov, pričom vychádza z vedeckých dôkazov.

# Oblasti extrapolácie

- Podskupiny populácie
  - Vek (pediatrická/geriatrická populácia)
  - Pohlavie, tehotenstvo
  - Komorbidity
  - Etnikum
- Podtypy/štádiá choroby; podobné (ale odlišné) choroby
- Lieky (vnútri/medzi skupinami)
- Druhy (predklinické testovanie)
- Komorbidity

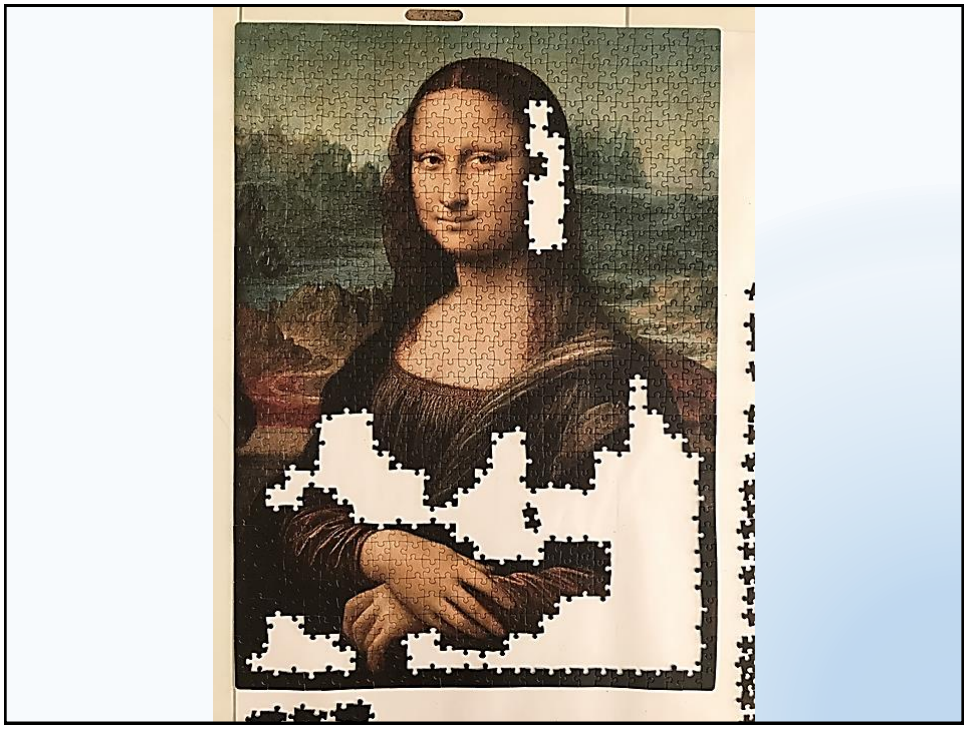
# Extrapolácia

- na potvrdenie biosimilarity
- zložitý proces
- nie automatický prenos tvrdenia o všetkých indikáciách REF na BSM
- vplyv viacerých faktorov
- rovnaký MÚ nie je automatické potvrdenie možnosti extrapolácie
- čím komplikovanejší mechanizmus (závislý od viacerých receptorov alebo väzobných miest ligandu), tým ťažšie extrapolovať
- ak je mAb odlišná alebo neznáma, extrapolačný proces je ešte komplikovanejší a vyžadujú sa ďalšie funkčné a/alebo klinické údaje
- Princíp schválenia na základe *„the totality of the data“*

# Zdôvodnenie

❖Vyhnúť sa „nepotrebným“ štúdiám

- Etika (štúdia na vulnerabilnej populácii; zdržanie/obmedzenie dostupnosti liečby)
- Efektivita (ďalšie typy štúdií, navyšovanie počtu pacientov)
- Alokácia zdrojov (sústredenie sa na oblasti, kde sú štúdie potrebné)



# Komplikácie extrapolácie

| Extrapolation difficulty | MOAs | Measures of effectiveness | Examples |
|---|---|---|---|
| Difficult | Very complex<br>Not well understood | Mortality<br>Progression free survival | Trastuzumab |
| Intermediate | Multiple mechanisms<br>Not as well understood | Clinical measures of disease activity | Infliximab |
| Easy | Simple<br>Well understood | PD or surrogate markers | Epoetin |

Agarwal AB, McBride A. Crit Rev Oncol Hematol. 2016;104:98-107

PD - progressive disease

# 1. generácia biosimilárov

- prvé biosimiláry odporučené CHMP EMA boli substancie s relatívne nízkou molekulovou hmotnosťou a jedným aktívnym miestom s väzbou na receptor špecifickým pre terapeutickú indikáciu (2x somatropín, 5x **epoetín** a 7x **filgrastim**)
- filgrastim a epoetín-alfa - prvé biosimiláry v hematologicko-onkologickej liečbe
- v začiatkoch iba pozvoľná akceptácia v praxi, iniciálny nedostatok dôvery
- použitie: najmä substitučná liečba, podporná liečba

# 2. generácia biosimilárov

- Druhá vlna v roku 2013, molekuly so zložitými štruktúrami – monoklonálne protilátky a fúzne proteíny
- Nové výzvy:

- viacero väzobných miest, pre viacero receptorov
- chorobu modifikujúce liečivá
- originály majú schválené rôznorodé indikácie
- extrapolácia oveľa zložitejšia, ak nie nemožná
- potreba špecifických a (hlavne) prísnejších usmernení pre klinické testovanie a hodnotenie imugenicity
- 700 produktov v predklinickej alebo klinickej fáze

# Prípad rituximab

- rozmanité indikácie:
  - Non-Hodgkinov lymfóm (NHL)
  - Reumatoidná artritída
  - Granulomatóza s polyangiitídou a mikroskopická polyangiitída
- podobné obavy - extrapolácia údajov z klinických štúdií biosimilátorov rituximabu
- z jedného klinického prostredia do iného

1) rôzne ochorenia (reumatoidná artritída, folikulárny lymfóm)
2) rôzne histologické podtypy NHL
3) paliatívnych vs. liečebných stratégií NHL
4) kombinovaných režimov (s chemoterapiou) vs. monoterapia NHL

# Vedecké zdôvodnenie

- selekcia populácie – potreba dostatočne senzitívnej indikácie na detekciu prípadných klinicky významných odlišnosti medzi BSM a REF
- dlhodobé užívanie rituximabu a množstvo poznatkov v indikácii reumatoidná artritída (RA)
- dostatočné množstvo dát u folikulárneho lymfómu (FL), je možná predikcia
- podobnosť v patogenéze ochorenia (akumulácia B buniek)
- MÚ rituximabu – zacielený proti markeru CD20 na B bunkách
- 1 štúdia fázy I (bezpečnosť a PK u pacientov s B-bunkovým non-Hodgkinovým lymfómom) + 2 štúdie fázy III (PK/PD, bezpečnosť a účinnosť u RA a FL)
- **Záver:** Extrapolácia PK/PD údajov u pacientov s RA a FL je akceptovateľná na iné onkologické a autoimúnne chorobné stavy

Table 2. Comparative efficacy clinical trials of proposed biosimilars of bevacizumab, rituximab and trastuzumab: study design, population, primary end point, type of margin and efficacy results.

| Biosimilar candidate (manufacturer; trade name) | Clinical trial name, NTC identifier | Study design | RMP source | Patient population Line treatment | n | Efficacy | | | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Primary end point Analysis population | Type of margin (E or NI) | Results: RR or RD (CI) | |
| **Bevacizumab candidates (Avastin®) indicated for metastatic carcinoma of colon or rectum, MBC, NSCLC, metastatic renal cell cancer, metastatic carcinoma of cervix, epithelial ovarian, fallopian tube or primary peritoneal cancer¶** | | | | | | | | | |
| ABP 215 (Amgen; Mvasi®) | Study 20120265 NCT01966003 | Multicenter, double-blind, randomized | EU | Advanced NSCLC Combination with P + C | 642 | Objective response rate at 19 weeks ITT | E for RR: 0.67, 1.5 (90% CI) | RR: 0.93 (0.80; 1.09) | [41] |
| BCD-021 (Biocad; Avegra®) | NCT01763645 | Multicenter, double-blind, randomized | EU | Advanced NSCLC Combination with P + C | 138 | Overall response rate at day 127 Unknown | NI | RD: 3.3% (-14.96%) | [42] |
| BI 695502 (Boehringer Ingelheim) | NCT02272413 | Multicenter, double-blind, randomized | USA | Advanced NSCLC Combination with P + C | 671 | Best overall response rate at 19 weeks PPS | E for RR: 0.736, 1.359 (90% CI) E for RR: 0.736, 1.359 (95% CI) | RR: 0.855 (90% CI: 0.7697; 0.9506) (95% CI: 0.7543; 0.9700) | [43] |
| FKB238 (Centus Biotherapeutics Ltd; Equidacent®) | AVANA NCT02810457 | Multicenter, double-blind, randomized | EU | Advanced or recurrent NSCLC Combination with P + C | 731 | Overall response rate at 19 weeks PPS | E for RD: ±0.1221 (95% CI) | RD: 0.02 (95% CI: -0.0905, 0.0568) | [44] |
| MB02 (mAbxience/STADA) Alymsys® /Oyavas®) | STELLA trial NCT03296163 | Multicenter, double-blind, randomized | EU | Stage IIIB/IV NSCLC Combination with P + C | 627 | Objective response rate at 18 weeks ITT | E for RD: ±12% (95% CI) | RD: -4.02 (-11.76, 3.71) | [45,46] |
| PF-06439535 (Pfizer; Zirabev®) | Study B7391003 NCT02364999 | Multicenter, double-blind, randomized | EU | Advanced NSCLC Combination with P + C | 719 | Objective response rate at week 25 ITT | E for RD: ±13% (95% CI) E for RR: 0.73–1.37 (90% CI) E for RR: 0.729–1.371 (95% CI) | RD: 0.653% (6.608; 7.908) RR: 1.015 (95% CI: 0.863; 1.193) (90% CI: 0.886; 1.163) | [47] |
| SB-8 (Samsung Bioepis, Aybintio®) | NCT02754882 | Multicenter, double-blind, randomized | EU | Metastatic or recurrent NSCLC Combination with P + C | 763 | Best objective response rate at 24 weeks PPS | E for RD: ±12.5% (95% CI) E for RR: 0.737, 1.357 (90% CI) | RD: 5.3% (-2.2%, 12.7%) RR: 1.12 (0.977, 1.278) | [48] |
| **Rituximab candidates (Mabthera®) indicated for CLL and NHL including (FL and DLBCL)¶** | | | | | | | | | |
| ABP798 (Amgen; Riabni®) | JASMINE NCT02747043 | Double-blind, randomized | | Grade I, II, IIIa FL and LTB-FL Combination with standard chemotherapy of local center | 256 | Overall response rate (CR + PR) at week 28 PPS | NI: -15% (95% CI) | RD: -1.4% (-3.2%; 18.6%) | [49] |

† Based on local review.
‡ Based on central independent review.
§ Primary end point was a PK parameter (percentage of patients with trough plasma concentration $C_{trough}$ >20 μg/ml at cycle 5).
¶ Oncologic indications approved by the EMA/EC.
bpCR: Breast pathological complete response; CLL: Chronic lymphocytic leukemia; CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisone; CR: Complete response; CVP: Cyclophosphamide, vincristine and prednisone; D: Docetaxel; D + C: Docetaxel and carboplatin; DLBCL: Diffuse large B cell non-Hodgkin's lymphoma; E: Equivalence; EBC: Early breast cancer; EC: European Commission; EU: Europe; FC: Fludarabine and cyclophosphamide; FEC-D: Fluorouracil, epirubicin, cyclophosphamide and docetaxel; FL: Follicular lymphoma; ITT: Intention-to-treat; LTB: Low tumor burden; MBC: Metastatic breast cancer; mITT: Modified intention-to-treat; NHL: Non-Hodgkin lymphoma; NI: Non-inferiority; NS: Not specified; NSCLC: Non-small-cell lung cancer; ORR: Overall response rate; P: Paclitaxel; P + C: Paclitaxel and carboplatin; P/D: Paclitaxel or docetaxel; PK: Pharmacokinetic; PPS: Per protocol set; PR: Partial response; RD: Risk difference; RMP: Reference medicinal product; RP: Reference product; RR: Risk ratio; tpCR: Total pathological complete response (breast + lymph nodes).

Table 2. Comparative efficacy clinical trials of proposed biosimilars of bevacizumab, rituximab and trastuzumab: study design, population, primary end point, type of margin and efficacy results (cont.).

| Biosimilar candidate (manufacturer; trade name) | Clinical trial name, NTC identifier | Study design | RMP source | Patient population Line treatment | n | Efficacy | | | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Primary end point Analysis population | Type of margin (E or NI) | Results: RR or RD (CI) | |
| BCD-020 (Biocad; Acellbia®) | NCT01701232 | Multinational, randomized, open-label | EU | Grade I/II FL | 174 | Overall response rate (CR + PR) at day 50 Unknown | E: ±20% (95% CI) | RD: 2.82% (-12.62%; 18.24%) | [50] |
| CT-P10 (Celltrion Healthcare; Truxima® /Blitzima® / Ritemvia®) | Study CT-P10 3.3 NCT02162771 | Randomized, double-blind, | USA | Advanced FL Combination with CVP | 140 | Overall response rate at 12 weeks PPS | NI: -7% (97.5% CI) | RD: 4.3%; (-4.25) | [51] |
| | Study CT-P10 3.4 NCT02260804 | Randomized, double-blind, | USA | LTB-FL | 258 | Overall response rate at 7 months ITT | E: ±17% (90% CI) | RD: 1.8% (-6.43; 10.20) | [52] |
| GP2013 (Sandoz; Rixaton®/Riximyo®) | Study ASSIST-FL NCT01419665 | Multinational, double-blind, randomized | EU | Advanced FL Combination with CVP | 629 | Overall response rate at 24 weeks PPS | E: ±12% (95% CI) | RD: -0.40% (-5.94; 5.14) | [53] |
| HLX01 (Henlius) | NCT02787239 | Multicenter, randomized, double-blind | EU | DLBCL Combination with CHOP | 407 | Overall response rate at 6 cycles PPS | E: ±12% (95% CI) | RD: 1.4% (-3.59, 6.32) | [54] |
| PF-05280586 (Pfizer; Ruxience™) | REFLECTIONS B328-06 NCT02213263 | Multinational, randomized, double-blind, | EU | LTB-FL | 394 | Overall response rate (CR + PR) at 26 weeks ITT | E: ±16% (95% CI) | RD: 4.66%; (-4.16; 13.47) | [55] |
| RTXM83 (mAbxience; Novex®) | RTXM83-AC-01-11 NCT02268045 | Multicenter, double-blind, randomized | EU | DLBCL Combination with CHOP | 272 | Overall response rate (CR + PR) at 16 weeks PPS | NI: -13% (95% CI) | RD: 0.7% (-8.77%) | [56] |
| (AryoGen Pharmed; Zytux™) | | Double-blind, randomized | EU | CLL Combination with FC | 70 | Overall response rate (CR + PR) PPS | NI: -20% (95% CI) | RD: 1% (-17%) | [57] |
| **Trastuzumab candidates (Herceptin®) indicated for EBC, MBC and metastatic gastric cancer¶** | | | | | | | | | |
| ABP 980 (Amgen; Kanjinti®) | LILAC study NCT01901146 | Multicenter, randomized double-blind | EU | Neoadjuvant + adjuvant EBC Combination with P | 725 | tpCR ITT | E for RD: ±13% (90% CI) E for RR: 0.759, 1.318 (90% CI) | RD: 7.3% (1.2, 13.4)† 5.8% (-0.5, 12.0)‡ RR: 1.19 (1.033, 1.366)† 1.14 (0.993, 1.312)‡ | [58] |

† Based on local review.
‡ Based on central independent review.
§ Primary end point was a PK parameter (percentage of patients with trough plasma concentration $C_{trough}$ >20 μg/ml at cycle 5).
¶ Oncologic indications approved by the EMA/EC.
bpCR: Breast pathological complete response; CLL: Chronic lymphocytic leukemia; CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisone; CR: Complete response; CVP: Cyclophosphamide, vincristine and prednisone; D: Docetaxel; D + C: Docetaxel and carboplatin; DLBCL: Diffuse large B cell non-Hodgkin's lymphoma; E: Equivalence; EBC: Early breast cancer; EC: European Commission; EU: Europe; FC: Fludarabine and cyclophosphamide; FEC-D: Fluorouracil, epirubicin, cyclophosphamide and docetaxel; FL: Follicular lymphoma; ITT: Intention-to-treat; LTB: Low tumor burden; MBC: Metastatic breast cancer; mITT: Modified intention-to-treat; NHL: Non-Hodgkin lymphoma; NI: Non-inferiority; NS: Not specified; NSCLC: Non-small-cell lung cancer; ORR: Overall response rate; P: Paclitaxel; P + C: Paclitaxel and carboplatin; P/D: Paclitaxel or docetaxel; PK: Pharmacokinetic; PPS: Per protocol set; PR: Partial response; RD: Risk difference; RMP: Reference medicinal product; RP: Reference product; RR: Risk ratio; tpCR: Total pathological complete response (breast + lymph nodes).

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Primary end point Analysis population | Type of margin (E or NI) | Results: RR or RD (CI) | |
| BCD-022 (Biocad; Herticad®) | NCT01764022 | Multicenter, randomized double-blind | EU | MBC Combination with P | 225 | Overall response rate mITT | E for RD: -20% (95% CI) | RD: 6.0%% (-8.05%, 19.89%) | [59] |
| CT-P6 (Celltrion Healthcare; Herzuma®) | Study CT-P6 3.2 NCT02162667 | Randomized, double-blind | USA | Neoadjuvant + adjuvant EBC Combination with FEC-D | 549 | tpCR ITT | E for RD: ±0.15 (95% CI) E for RR: 0.74, 1.35 (95% CI) | RD: -0.04 (-0.12, 0.05) RR: 0.93 (0.78, 1.11) | [60] |
| | NCT01084876 | Randomized, double-blind | USA | MBC Combination with P | 475 | Overall response rate ITT | E: ± 0.15 (95% CI) | RD: 5% (-0.14, 0.04) | [61] |
| HLX02 (Accord Healthcare, Zercepac) | NCT03084237 | Randomized, double-blind | EU | MBC Combination with D | 649 | Overall response rate at week 24 ITT | E: ± 13.5% (95% CI) | RD: -0.4% (-7.4; 6.6) | [62] |
| MYL-1401O (Mylan; Ogivri®) | HERiTAge NCT02472964 | Randomized, double-blind | EU | MBC Combination with P/D | 500 | Best overall response rate ITT | E for RD: ±15% (95% CI) E for RR: 0.81, 1.24 (90% CI) | RD: 5.53 (-3.08, 14.04) RR: 1.09 (0.974, 1.211) | [63] |
| PF-05280014 (Pfizer; Trazimera®) | REFLECTIONS B327-02 NCT01989676 | Multinational, randomized, double-blind | EU | MBC Combination with P | 707 | Objective response rate (CR + PR) at 25 weeks ITT | E for RR: 0.8, 1.25 (95% CI) | RR: 0.940 (0.842, 1.049) | [64] |
| | REFLECTIONS B327-04 NCT02187744 | Multinational, randomized, double-blind | EU | Neoadjuvant + adjuvant EBC Combination with D + C | 226 | tpCR and objective response rate§ PPS | NS | RD (pCR): -2.81% (-16.58; 10.96)RD (ORR): 5.96% (-4.01; 15.94) | [65] |
| SB3 (Samsung Bioepis, Ontruzant®) | NCT02149524 | Multicenter, randomized double-blind | EU | Neoadjuvant + adjuvant EBC Combination with FEC-D | 800 | bpCR PPS | E for RD: ±13% (95% CI) E for RR: 0.785, 1.546 (95% CI) | RD: 10,70% (4.13, 17.26) RR: 1.259 (1.085, 1.460) | [66] |

†Based on local review.
‡Based on central independent review.
§Primary end point was a PK parameter (percentage of patients with trough plasma concentration $C_{trough}$ >20 μg/ml at cycle 5).
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Assessment of rituximab-abbs, a biosimilar, and rituximab outcomes in patients with CLL or NHL: A real-world UK study

Ali McBride [a,*], Shoshana Daniel [b], Maurice T. Driessen [c], Agota Szende [d], Azhar Choudhry [e], Marc Tian [e], Rinat Arielyˈ [f], Stephen Thompson [f]

*Conclusion:* Rituximab-abbs and rituximab demonstrated similar effectiveness and tolerability in treating CLL and NHL in routine UK clinical practice and demonstrate the utility of the biosimilar as a cost-saving alternative treatment.



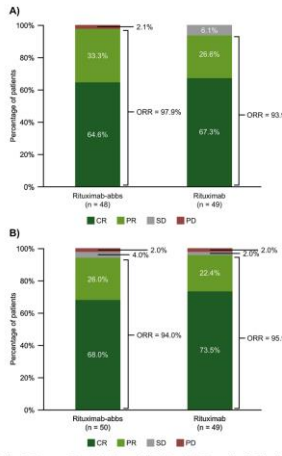



**Fig. 2.** Response Rate in Patients with CLL or NHL Treated with Rituximab-Abbs or Rituximab. (A) response rate in patients with CLL. (B) response rate in patients with NHL.
Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete response; NHL = non-Hodgkin lymphoma; PD = progressive disease; PR = partial response; SD = stable disease

**Table 2**
Tolerability as Assessed by the Occurrence of Pre-Specified Treatment-Emergent Adverse Events Related to Rituximab/Rituximab-Abbs Administration.

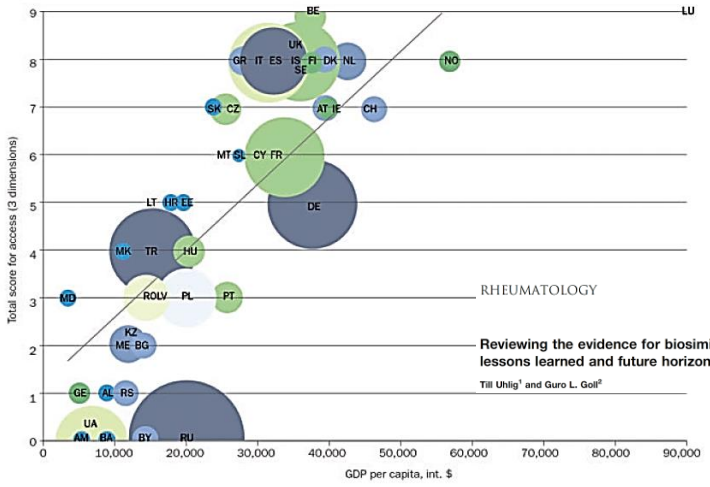
| Grade ≥3 TEAEs | CLL | | NHL | |
|---|---|---|---|---|
| | Rituximab-Abbs (n = 51) | Rituximab (n = 50) | Rituximab-Abbs (n = 50) | Rituximab (n = 50) |
| Number of TEAEs | | | | |
| Mean (SD) | 1.1 (1.6) | 1.2 (2.2) | 1.4 (1.9) | 0.9 (1.8) |
| Median (IQR) | 0 (0–2) | 0 (0–2) | 0 (0–2) | 0 (0–1) |
| TEAE, n (%)[a] | | | | |
| Infusion reaction | 8 (16) | 3 (6) | 8 (16) | 6 (12) |
| Tumor lysis syndrome | 0 | 1 (2) | 0 | 0 |
| Pain | 1 (2) | 0 | 3 (6) | 0 |
| Fatigue | 9 (18) | 8 (16) | 13 (26) | 5 (10) |
| Anemia | 7 (14) | 10 (20) | 10 (20) | 6 (12) |
| Peripheral neuropathy | 0 | 0 | 1 (2) | 1 (2) |
| Nausea | 5 (10) | 7 (14) | 8 (16) | 3 (6) |
| Neutropenia | 11 (22) | 10 (20) | 8 (16) | 8 (16) |
| Constipation | 1 (2) | 1 (2) | 1 (2) | 2 (4) |
| Diarrhea | 2 (4) | 4 (8) | 2 (4) | 4 (8) |
| Vomiting | 2 (4) | 2 (4) | 2 (4) | 2 (4) |
| Cancer-related hospitalization | 0 | 1 (2) | 0 | 0 |
| Neutropenic sepsis | 3 (6) | 2 (4) | 2 (4) | 3 (6) |
| Pyrexia | 3 (6) | 4 (8) | 3 (6) | 2 (4) |
| Troponin increased | 0 | 0 | 0 | 0 |
| Dyspnea | 0 | 0 | 2 (4) | 0 |
| Decreased appetite | 1 (2) | 3 (6) | 2 (4) | 1 (2) |
| Stomatitis | 2 (4) | 0 | 2 (4) | 0 |
| Weight decrease | 0 | 2 (4) | 1 (2) | 1 (2) |
| Back pain | 0 | 1 (2) | 0 | 0 |
| None of the above | 28 (55) | 31 (62) | 27 (54) | 33 (66) |

Abbreviations: CLL = chronic lymphocytic leukemia; IQR = interquartile range; NHL = non-Hodgkin lymphoma; SD = standard deviation; TEAE = treatment emergent adverse events.
[a] Percentages may sum to more than 100 % as patients may have had more than 1 treatment-emergent adverse event.

*Chronic lymphocytic leukemia (CLL)*
*Non-Hodgkin lymphoma (NHL*

# Integrácia biosimilárov do farmakoterapie v EU

FIG. 3 Access to biologic DMARDs according to gross domestic product per capita




RHEUMATOLOGY

**Reviewing the evidence for biosimilars: key insights, lessons learned and future horizons**

Till Uhlig[1] and Guro L. Goll[2]

REGULAR ARTICLE

blood advances

## Impact of rituximab biosimilars on overall survival in diffuse large B-cell lymphoma: a Dutch population-based study

Mirian Brink,[1] Xaver U. Kahle,[2] Joost S. P. Vermaat,[3] Josee M. Zijlstra,[4] Martine Chamuleau,[4] Marie José Kersten,[4] Müjde Durmaz,[1] Wouter J. Plattel,[2] Pieternella J. Lugtenburg,[5] Wendy Stevens,[6] Rogier Mous,[7] Elisabeth G. E. de Vries,[8] Marjolein W. M. van der Poel,[9] Prashant V. Nannan Panday,[10] Gerwin Huls,[2] Tom van Meerten,[3] and Marcel Nijland[2]

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The full-text version of this article contains a data supplement.




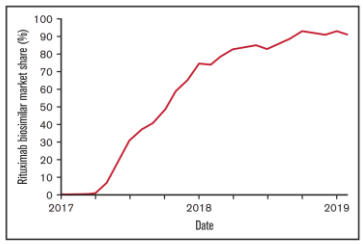


**Figure 1. Pace of conversion of rituximab originator (R-originator) to rituximab biosimilars (R-biosimilars) in the Netherlands.** Line graph depicting the market share of rituximab biosimilars from their approval by the European Medicines Agency in 2017 until January 2019.

Research Article
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Future ONCOLOGY

# Real-world use and acceptance of biosimilar monoclonal antibodies of rituximab in oncology practice in the USA

Ahmed Shelbaya[1,2], John M Kelton[1], Jeffrey Thompson[3], Jose MJ Alvir[4], Martine C Maculaitis[1] & Jingyan Yang[1,5]
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**Lay abstract:** A biosimilar is a biological medication that is highly similar in structure and function to a biological medication already approved by the US FDA – the 'original biologic'. The first biosimilars approved to treat certain blood cancers have become available in the USA. This study examined how a recently introduced rituximab biosimilar was being utilized, looking at patient and physician characteristics from a medical and prescription insurance claims database. This study did not examine the safety or effectiveness of this medication. While initial data are limited, the biosimilar, rituximab-pvvr, appears to be utilized to treat the same types of cancer as the original biologic, rituximab. The biosimilar was most frequently prescribed for non-Hodgkin's lymphoma and chronic lymphocytic leukemia.

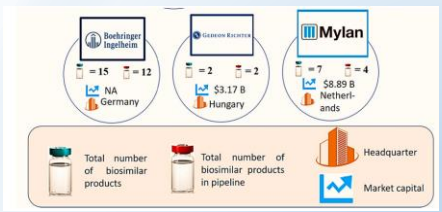
## Summary points

- Biosimilars are anticipated to improve treatment access and reduce costs associated with cancer treatment.
- The recently introduced biosimilar monoclonal antibody rituximab-pvvr is US FDA approved for use in reference product cancer indications.
- This retrospective analysis of pharmacy claims data, covering the period between 1 January 2019 and 31 July 2020, included 249 patients aged ≥18 years with one or more claims indicating usage of the rituximab-pvvr biosimilar.
- Rituximab-pvvr was most commonly used for treating patients with non-Hodgkin's lymphoma (NHL; n = 193, 77.5%) and chronic lymphocytic leukemia (CLL; n = 28, 11.2%).
- Rituximab-pvvr prescribers primarily specialized in hematology oncology (54.2%) and were in practice in the south of the USA (59.0%).
- Switching to rituximab-pvvr from the reference product or another rituximab biosimilar was observed in 42.5 and 39.3% of patients with NHL and CLL, respectively.
- Nearly two-thirds (63.2%) of patients with NHL and 50.0% of those with CLL were receiving chemotherapy in combination with rituximab-pvvr; rituximab-pvvr was also used concurrently with targeted therapy or immunotherapy.
- Exploratory analysis showed statistically significant differences in patient region of residence, as well as provider type and region of practice, when comparing rituximab-pvvr and the reference product.
- Given that rituximab-pvvr was only recently introduced in the USA, analysis of longitudinal trends in uptake and assessment of cost–effectiveness will require further research with a longer-term follow-up period.

# Ďalšie perspektívy biosmilárov v onkológii

U 20 onkologických biologických liekov expiruje ochrana exkluzivity dát do 2023
2023-2024 – „veľký tresk" biosimilárov v onkológii




Biosimilárne lieky v pipeline.

## Záver

- Overená a potvrdená vysoká **funkčnosť konceptu** biosimilárov v onkológii
- Potvrdená účinnosť a bezpečnosť *in real world*
- Akumulácia množstva poznatkov v oblasti výroby a kvality
- Robustný regulačný systém
- Dlhoročné klinické skúsenosti
- Globálny (špeciálne EÚ) záujem

# Ďakujem za pozornosť