A $trategic $ummary of Biologic Agent$

A Penny for your Thought$

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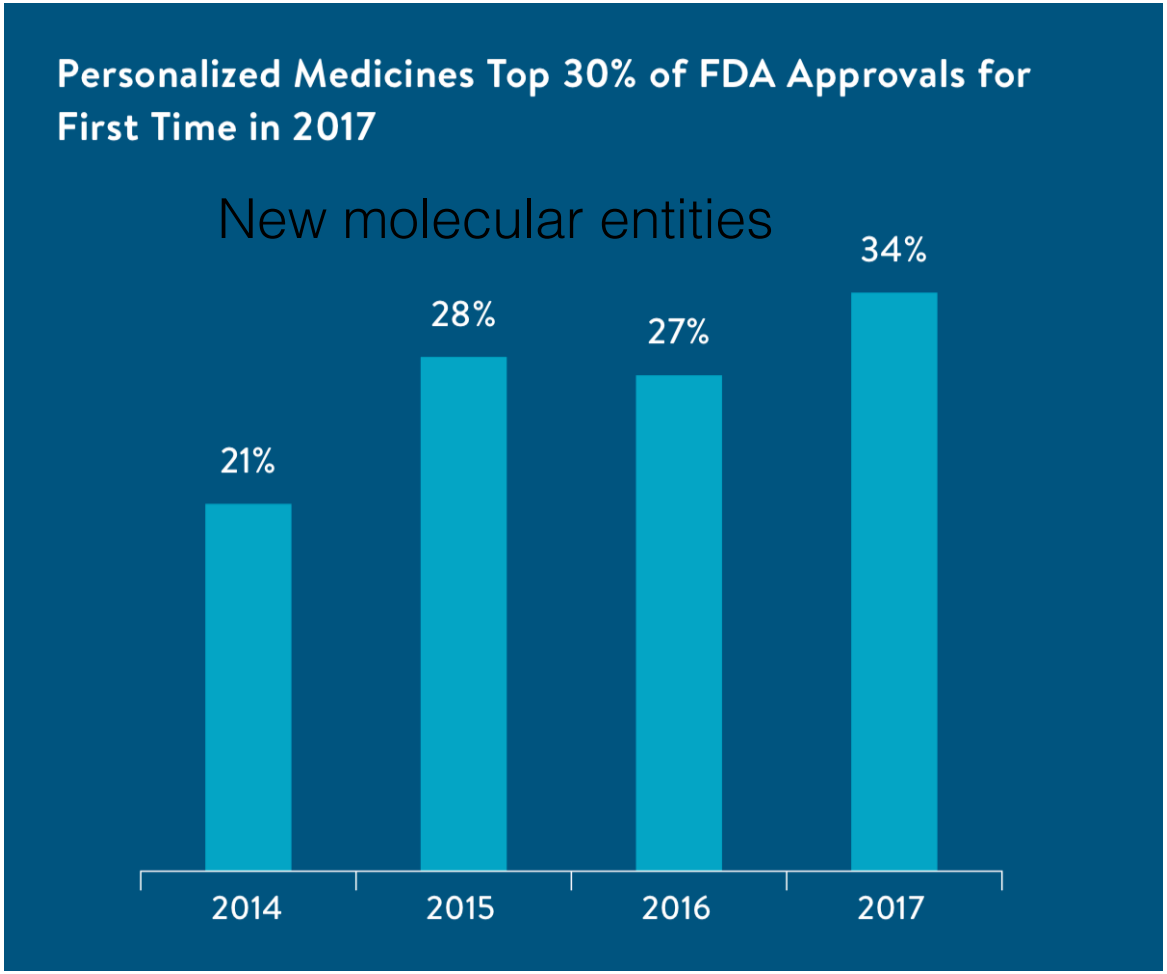
biologic agents are a product produced from living organisms or contain components of living organisms

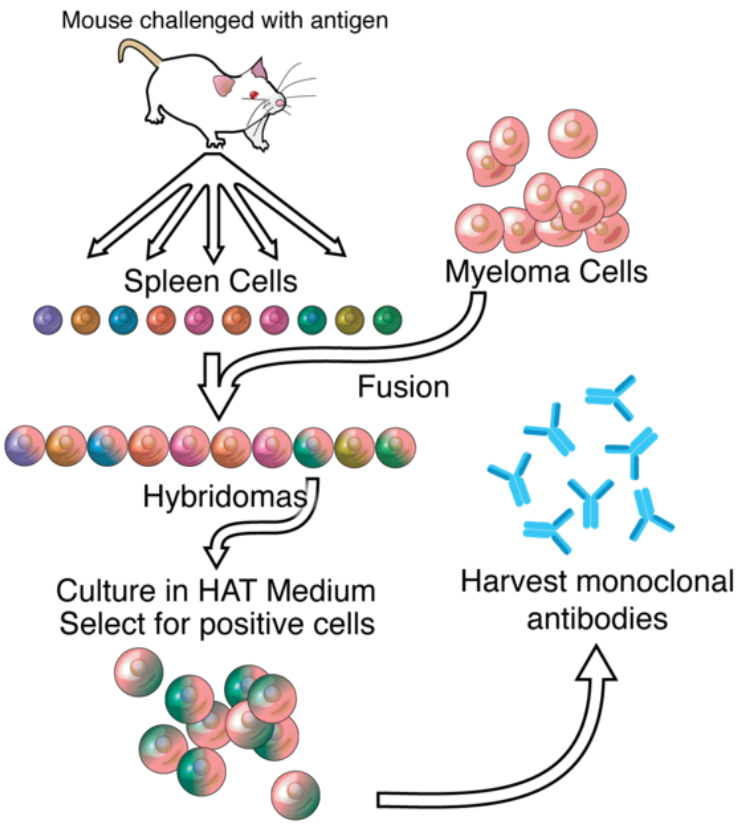
therapeuticseducation.org
medicationmythbusters.com



16 Total

Cancer x 9
Hep C x 2
Huntington's
Tardive dyskinesia
Batten disease
Mucopolysaccharidosis
Hemophilia

Design antibodies to target a specific antigen - **monoclonal antibodies**



Nomenclature

all end in -mab

Then source

-a-mab = rat
-e-mab = hamster
-o-mab = mouse
-u-mab = human
-zu-mab = humanized
-xi-mab = chimeric(hum/non-human)

Then target

-ci- = circulatory
-ba- = bacterium
-li- = immune system
etc

1986 - first licenced monoclonal antibody Orthoclone OKT3 (muromonab-CD3) preventing kidney transplant rejection

FDA1997 - Rituximab - cancer, RA

first monoclonal antibody to receive FDA approval for cancer therapy - relapsed or refractory low grade or follicular B-cell non-Hodgkin lymphoma

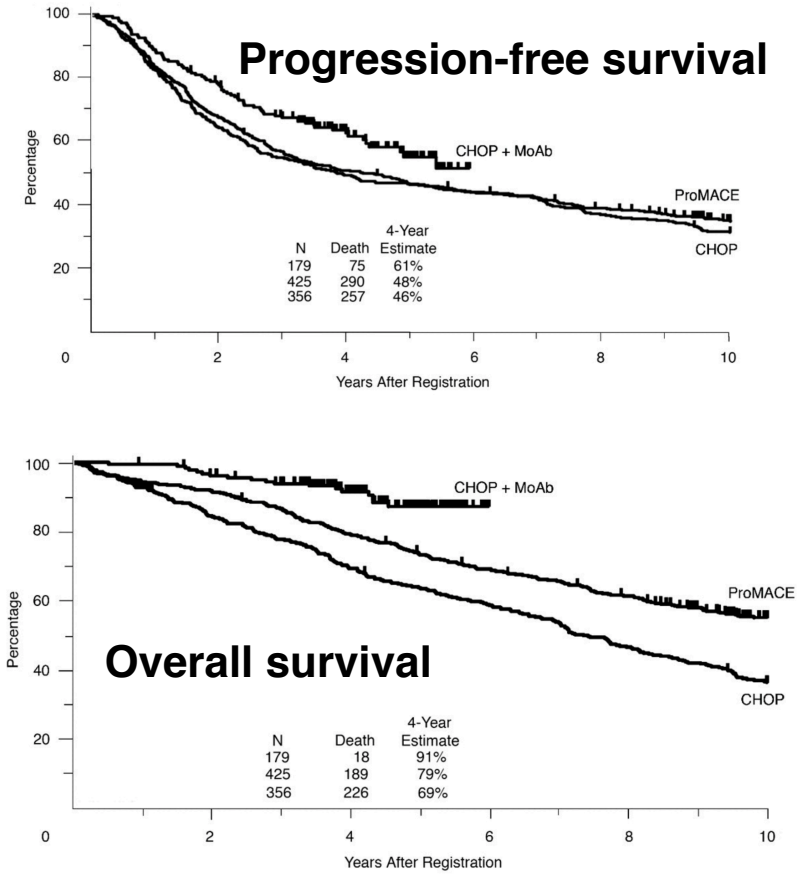
166 patients - “heavily” treated relapsed low-grade lymphoma - 48% responded - “toxicity was mild”

~80-90% infusion reactions, ~10-15% Grade 3/4 cytopenias - case reports of many different types of infections

“The response rate of 48% is comparable to results with single-agent cytotoxic chemotherapy”

Journal of Clinical Oncology 1998;8:2825-33

Observational data



Addition of rituximab
~15% benefit
at 4 years

Overall survival
likely also reflects better supportive care and possibly the selection of patients earlier in their disease

Addition of rituximab
~10% benefit
at 4 years

J Clin Oncol 2005;23:8447– 8452

6 non-cancer examples

Treatments that reduce risk

Palivizumab - severe RSV infection in children

Evolucumab - hyperlipidemia/heart disease

Romosozumab - fracture

Treatments that reduce symptoms

Guselkumab - plaque psoriasis

Dupilumab - uncontrolled persistent asthma

Erenumab for migraine

FOR NONE OF THESE IS THIS A SYNOPSIS OF ALL THE AVAILABLE EVIDENCE

MABs for risk reduction

Palivizumab for reducing the risk of severe RSV infection in children

bronchiolitis and pneumonia in children is most commonly caused by the Respiratory Syncytial Virus (RSV)

most infants recover from this virus but serious complications can occur, especially in those with underlying medical conditions such as congenital heart disease

Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children (Review)

palivizumab (Synagis®), a monoclonal antibody produced by recombinant DNA technology

3 placebo-controlled studies - 150 days - 5 monthly injections

infants and children at high risk of developing LRT disease caused by RSV, i.e. those with chronic lung disease (or bronchopulmonary dysplasia), congenital heart disease, immunodeficiency, chronic neuromuscular disease, congenital anomalies or those born preterm

RSV hospitalisations - RR 0.49, 95% CI 0.37 to 0.64

all-cause mortality - RR 0.69, 95% CI 0.42 to 1.15

serious adverse events - RR 1.04, 95% CI 0.96 to 1.13

CD006602-2013

BASELINE - placebo - 10% hospitalized over a 5-month period

10% reduced 50% - down to 5%

5-monthly injections cost ~ $10,000US

need cohorts for long term risk

Evolucumab for hyperlipidemia and reducing the risk of heart disease

FOURIER study

average age 63, 75% male, 85% Caucasian, 100% previous CVD

2.2 years

risk of a combined CVD endpoint (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization)

hazard ratio of 0.85 (0.79 to 0.92) - a 15% relative benefit

no reduction in mortality or serious adverse events

N Engl J Med 2017;376:1713-22

placebo - 11.3%, evolocumab - 9.8%

1.6% absolute benefit or NNT = 63

roughly $15,000 US a year

at present there is no information on the long-term benefits and harms of this agent

statins and/or medications used for blood pressure = 25-30% relative benefit

no head-to-head comparisons between these different treatments so comparisons are at best speculative

SPIRE - bococizumab - development stopped

50% developed antibodies

10 months - 63 y/o, 70% male, majority with CVD?,

LDL 2.8/109, 25% smokers, 93% on statins, 48% T2DM - n= ~27,000

	All deaths (%)	CVD death (%)	Nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, or unstable angina requiring urgent revascularization (%)	ADE resulting in drug D/C (%)	Injection site reaction (%)
Bococizumab	0.9	0.5	2.6	5.0	7.9
Placebo	0.9	0.5	2.9	3.4	1.0
RR	NSS			47	663
ARR				1.6	6.9
NNT/NNH				63	15

Lowered LDL 59% at 14 weeks, 47% at 52 weeks, raised HDL 6%

NEJM 2017

Romosozumab for fracture prevention

ARCH trial - ~ 4,100 subjects - women with previous fragility fracture

romosozumab or alendronate in a blinded fashion for 12 months followed by both receiving alendronate alone for 12 more months

24 months - RR 0.73 (0.61, 0.88)

clinical fractures - romosozumab 9.7%, alendronate 13%

3.3% absolute benefit - NNT 30 over alendronate

serious cardiovascular events - romosozumab 2.5%, alendronate 1.9% - NNH 167

also a 1.8% increase in injection site reactions

not yet marketed

N Engl J Med 2017; 377:1417-27

MABs for symptoms

Guselkumab used in the treatment of plaque psoriasis

Voyage 1 - 837 subjects moderate to severe psoriasis - 48 weeks

guselkumab vs adalimumab vs placebo (placebo crossed over to receive guselkumab - weeks 17-48)

PASI 90 - overall severity of psoriasis by combining the erythema, induration and desquamation with the percentage of the affected area

Quality of life scale - Index 0-30 with a higher score indicates worse disease13-14 - a change in 2-3 is considered a MICD

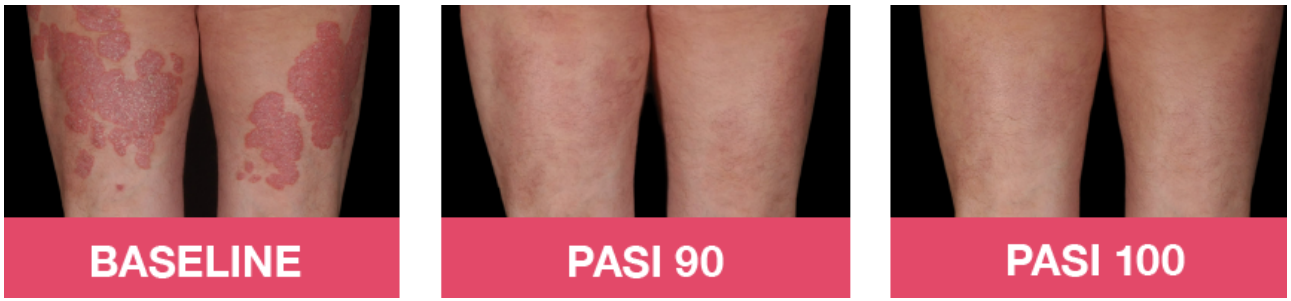
J Am Acad Dermatol 2017;76:405-17

PASI 90 - week 16

guselkumab 73%, adalimumab 50%, placebo 3%

Quality of life Index - started at 13-14
placebo - no change
treatment - improved (decreased) ~10 on treatment

malignancies and coronary events <1% in all groups



Dupilumab for uncontrolled persistent asthma

also used for eczema - 30-50% absolute increase in EASI-50

769 adult patients with uncontrolled persistent asthma despite ICs and LABA

4 different doses - 24 weeks - exacerbations and QOL (1-7 - started at 4)

exacerbations - placebo ~25%, monthly~15%, q2weeks ~10%

QOL - placebo increased by 0.9, dupilumab ~1.1-1.2
MICD is considered 0.5

Lancet 2016;388:31-44

exacerbations roughly 10-15% of people get a benefit over placebo

can’t evaluate if the drug is working because QOL for placebo subjects improved roughly the same amount in the dupilumab groups

Erenumab for episodic migraine

995 patients - 85% female, mean age 41, 56% no current or previous use of preventive treatment, 8.3 migraine days/ month

SQ 70 mg erenumab, 140 mg erenumab, placebo

After 4-6 months - 50% or greater reduction in the mean number of migraines/month

43% (70 mg), 50% (140 mg), 27% (placebo)

N Engl J Med 2017;377:2123-32

Other preventative agents

RESPONSE = ≥50% reduction in headache severity, frequency, or duration (usually assessed at 3 mos)

Across all high-quality trials 45% respond to drug, 24% will have response to placebo

6 examples

Treatments that reduce risk

Palivizumab - severe RSV infection in children

1 in 20 benefit

Evolucumab - hyperlipidemia/heart disease

1 in 63 benefit

Romosozumab - fracture

1 in 30 benefit, 1 in 167 harmed

Treatments that reduce symptoms

Guselkumab - plaque psoriasis

At least 1 in 2 benefit

Dupilumab - uncontrolled persistent asthma

1 in 10 benefit but they won't know

Erenumab for migraine

1 in 5 benefit - similar to other agents

Biologics or tofacitinib for people with rheumatoid arthritis naive to methotrexate: a systematic review and network meta-analysis (Review)

	Biologic PLUS MTX (%)	MTX (%)	Biologic (%)	MTX (%)
Improvement (ACR50)	56	40	35	37
Remission DAS <1.6 or DAS28 < 2.6	37	22	22	20
Withdrawal due to AE	7	5	6	6
SAE	11	10	3	7

CD012657 - 2017

Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA) (Review)

	Biologic (%)	Placebo (%)
Improvement (ACR50)	29	6
Remission (only 1 study)	95	85
Withdrawal due to AE	5	3
SAE	9	7

CD012437 - 2016

Long-term concerns

Infection

Cancer

Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis

Jasvinder A Singh, Chris Cameron*, Shahrzad Noorbaloochi, Tyler Cullis, Matthew Tucker, Robin Christensen, Elizabeth Tanjong Ghogomu, Doug Coyle, Tammy Clifford, Peter Tugwell, George A Wells*

absolute increase in the number of serious infections compared to DMARDs

standard dose - 6/1,000 per year

high dose - 17/1,000 per year

combination biological therapy - 55/1,000 per year

Lancet 2015;386:258–65

Cancer - psoriasis treatments

“There were important limitations to the studies identified including choice of comparator arms, inadequate adjustment for confounding factors and failure to account for latency periods of cancer. There remains a need for ongoing pharmacovigilance in relation to cancer risk and biological therapy”

Br J Derm Jan 2018

“Cumulative length of exposure to biological therapies in patients with psoriasis in real-world clinical practice does not appear to be linked to a higher risk of cancer after several years of use”

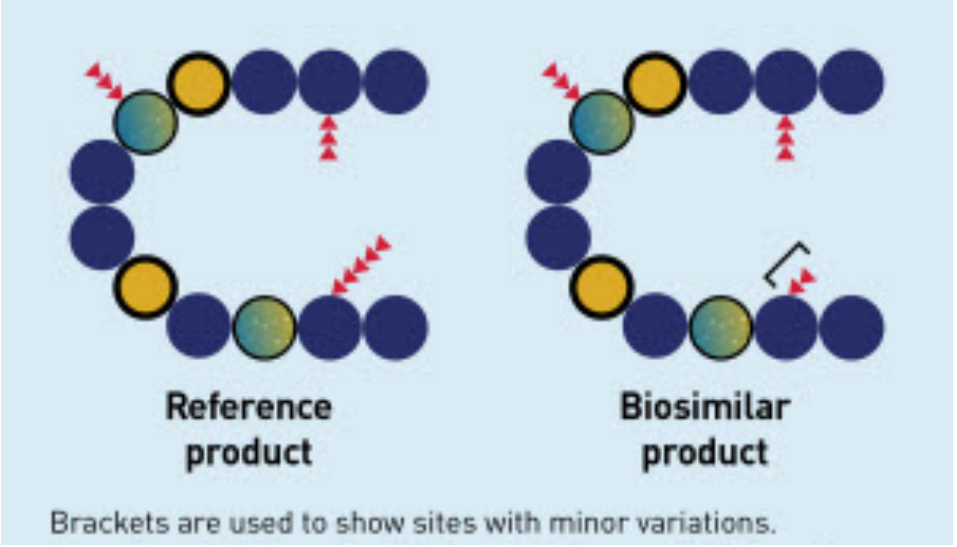
Br J Derm May 2018

Brand Name vs Generic
Biologics vs Biosimilars

Do these agents produce a similar:

Response

Risk of toxicity



Two Issues

Choosing between an originator or a biosimilar when starting therapy

Whether to switch from one to the other during established therapy

BioDrugs. 2017 Feb;31(1):1-36. doi: 10.1007/s40259-016-0207-0.

Biosimilars for the Treatment of Cancer: A Systematic Review of Published Evidence.

Jacobs I[1], Ewesuedo R[2], Lula S[3], Zacharchuk C[2].

Author information

"Under U.S. law, a biosimilar is approved based on a showing that it is 'highly similar' to an FDA-approved biological product, known as a reference product"

Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases

Jonathan Kay,[1] Monika M Schoels,[2] Thomas Dörner,[3] Paul Emery,[4] Tore K Kvien,[5] Josef S Smolen,[2,6] Ferdinand C Breedveld,[7] on behalf of the Task Force on the Use of Biosimilars to Treat Rheumatological Diseases

"The participants were confident that biosimilars approved by authorities in a highly regulated area are unlikely to differ from their bio-originators in clinically meaningful ways. Nevertheless, given the complex nature of all biopharmaceuticals, the treating clinician must be the only one to decide whether to prescribe a biosimilar in place of a bio-originator on a case-by-case basis with full awareness of the patient"

Ann Rheum Dis 2018;77:165–174

Typical Approach to Establishing Biosimilarity

A series of comparative studies with high face validity

analyses must demonstrate that the biosimilar and its bio-originator have the same primary amino acid sequence

no significant differences in charge isoforms, glycosylation, other post-translational modifications or impurities

there may be minor differences, but these must not affect critical quality attributes of the biologic

subsequent clinical studies must demonstrate PK and PD equivalence and equivalent efficacy in at least one disease for which the bio-originator is approved, as well as comparable safety and no greater immunogenicity of the biosimilar

Ann Rheum Dis 2018;77:165–174

Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes

Hillel P. Cohen[1] · Andrew Blauvelt[2] · Robert M. Rifkin[3] · Silvio Danese[4] · Sameer B. Gokhale[5] · Gillian Woollett[6]

"Thus, the extensive data collected to date suggest that the act of switching from a reference medicine to a biosimilar is not inherently dangerous"

"As with all biologics, continued pharmacovigilance is important to monitor for rare safety events and for unexpected changes in efficacy"

Drugs 2018;78:463-78

Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial

1st switch RCT - 482 patients - 52 weeks - infliximab or switch to a biosimilar - non-inferiority trial

Crohn's disease 32%, UC 20%, spondyloarthritis 19%, RA 16%, psoriasis 7%

Disease worsening - infliximab 26%, biosimilar 30% - 95%CI was -12.7%- 3.9% - did not include 15% non-inferiority margin

No suggestion of safety or immunogenicity differences

Lancet 2017;389:2304–16

A single issue of NEJM - Sept 25, 2018

ORIGINAL ARTICLE

First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

"the median overall survival was 12.3 months in the atezolizumab group and 10.3 months"

ORIGINAL ARTICLE

Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

"24-month overall survival rate was 66.3% in the durvalumab group, as compared with 55.6% in placebo"

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer

"the median overall survival was 15.9 months in the pembrolizumab-combination group and 11.3 months in the placebo-combination group"