Biosimilar Medicines

University of South Australia

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University of South Australia

RACP CONGRESS 2019
Aotea Centre,
Auckland, New Zealand,
6 – 8 May 2019
www.racpcongress.com.au

Biosimilar Medicines

Australian Government
Department of Health

Biosimilar Uptake Drivers

A biosimilar is a highly similar copy of an original or reference biological medicine. More information about biosimilar medicines is available on the Department's Biosimilar Awareness Initiative webpage.

What are the biosimilar uptake drivers?

The Australian Government supports initiatives to increase the use of biosimilar medicines.

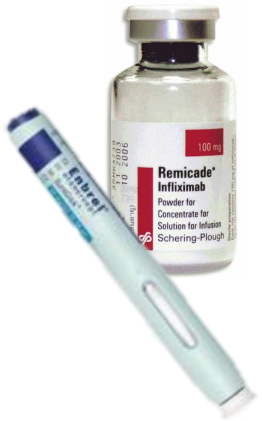
As part of the 2017 Budget process the Government reached agreement with Medicines Australia, the Generic and Biosimilar Medicines Association and the Pharmacy Guild of Australia to implement biosimilar uptake drivers.

Two specific biosimilar uptake drivers are being implemented:

- encouraging prescribing of a biosimilar brand rather than the reference biological brand for treatment naïve patients; and
- providing for a simpler and faster approval process for prescribing biosimilar brands (e.g. streamlined authority) while maintaining an existing higher level authority requirement for the reference biological brand (e.g. written authority).

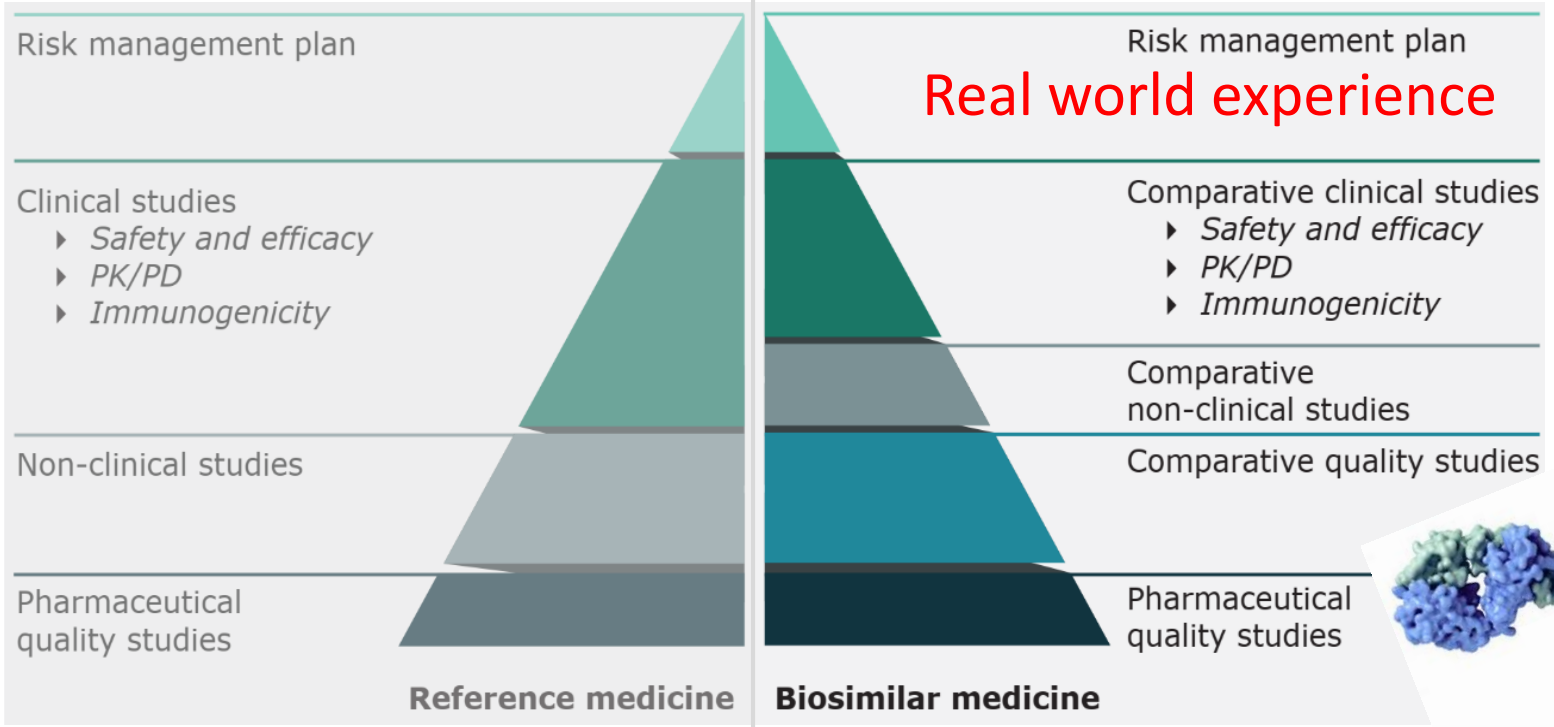
These uptake drivers are designed to supplement existing activities by the Department of Health to improve awareness of, and confidence in, biosimilars for both healthcare professionals and consumers.

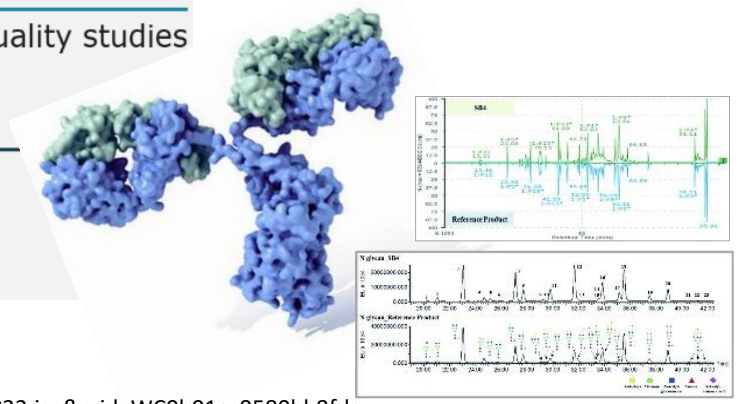
Biosimilar Development and Approval



demonstrating
safety & efficacy directly in
patients for the first time

demonstrating
comparable safety & efficacy
by establishing biosimilarity





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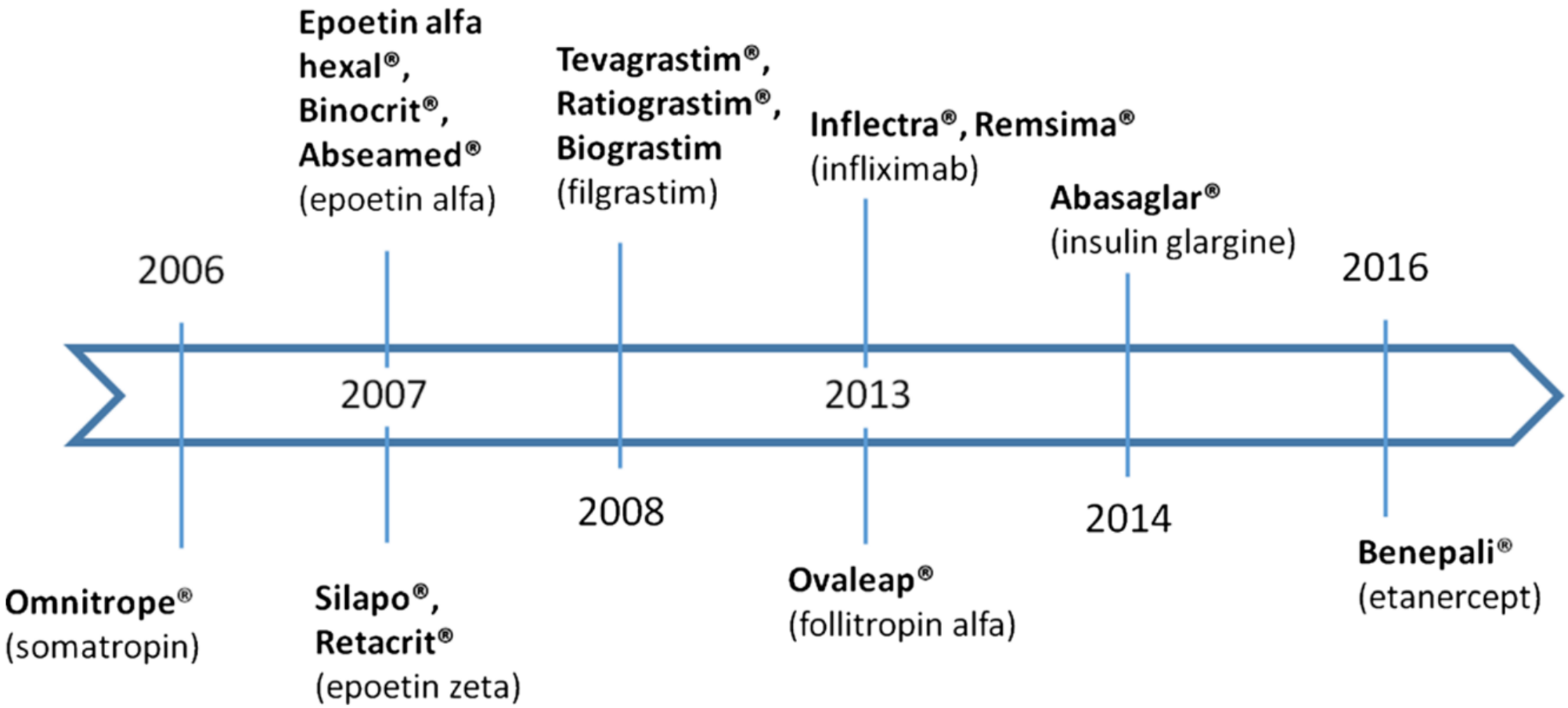
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_001832.jsp&mid=WC0b01ac0580bb8fda

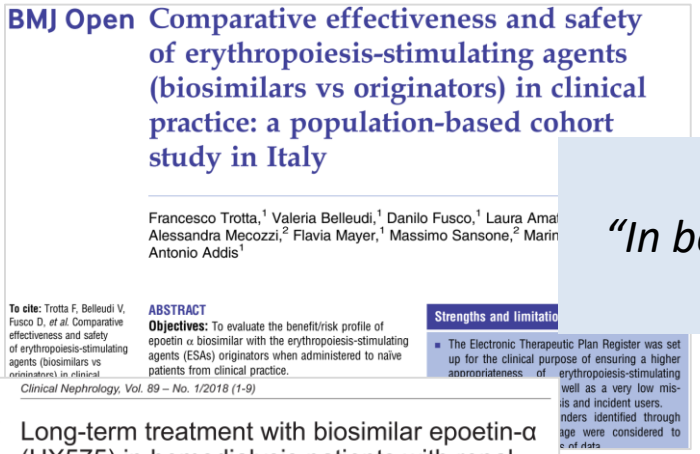
Global Biosimilar Approval Timeline



Araújo et al, Curr Rheumatol Rep (2016) 18: 50

Biosimilar Erythropoietin – real world experience

Representative conclusions of reported observational studies



BMJ Open

Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical practice: a population-based cohort study in Italy

Francesco Trotta,[1] Valeria Belleudi,[1] Danilo Fusco,[1] Laura Amat
Alessandra Mecozzi,[2] Flavia Mayer,[1] Massimo Sansone,[2] Marin
Antonio Addis[1]

To cite: Trotta F, Belleudi V, Fusco D, *et al*. Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical

ABSTRACT

Objectives: To evaluate the benefit/risk profile of epoetin α biosimilar with the erythropoiesis-stimulating agents (ESAs) originators when administered to naïve patients from clinical practice.

Strengths and limitatio

- The Electronic Therapeutic Plan Register was set up for the clinical purpose of ensuring a higher appropriateness of erythropoiesis-stimulating
well as a very low mis-
is and incident users.
nders identified through
age were considered to
s of data

Clinical Nephrology, Vol. 89 – No. 1/2018 (1-9)

clinical nephrology

Original

Long-term treatment with biosimilar epoetin-α (HX575) in hemodialysis patients with renal anemia: real-world effectiveness and safety in the MONITOR-CKD5 study

ISSN 0301-0430
DOI 10.5414/CN109245
e-pub: November 23, 2017

Gérard London[1], Johannes Mann[2], David Goldsmith
Frank Dellanna[5], Philippe Zaoui[6], Nadja Hoebel[7], Ar
Karen MacDonald[8], and Ivo Abraham[8,9]

[1]*Centre Hospitalier F.H. Manhés, Fleury-Mérogis, Fr*
Universität Erlangen-Nürnberg, Erlangen, Germany,
Foundation Hospital, London, UK, [4]*Centre Hospitali*
and Unité INSERM 1026, University of Bordeaux, B
[5]*Dialysezentrum, Düsseldorf, Germany,* [6]*Université*
[7]*Hexal AG, Holzkirchen, Germany,* [8]*Matrix45, Tucso*
[9]*University of Arizona College of Pharmacy, Tucson,*

Conclusion

*"In both settings, our findings are suggestive of **no difference** between biosimilars and originators on relevant effectiveness and safety outcomes."*

Conclusion

*"The MONITOR-CKD5 study of hemodialysis patients underscores the real-world effectiveness of HX575, a biosimilar epoetin-α, in managing renal anemia. Patients treated for up to 24 months with HX575 showed **Hb outcomes equivalent** to reference epoetin-α under dosing patterns similar to the reference medicine. The majority of treated patients were maintained within guideline-recommended target Hb ranges. **No unknown safety signals**, including immunogenicity, were detected."*

Biosimilar Erythropoietin – real world experience

Isolated observational studies with alternate findings

Clin Drug Investig (2017) 37:965–973
DOI 10.1007/s40261-017-0562-8

ORIGINAL RESEARCH ARTICLE

Effectiveness of Switch to Erythropoiesis-Stimulating Agent (ESA) Biosimilars versus Maintenance of ESA Originators in the Real-Life Setting: Matched-Control Study in Hemodialysis Patients

Roberto Minutolo[1] · Piergiorgio Bolasco[2] · Paolo Chiodini[3] · Stefano Sposini[4] · Maurizio Borzumati[5] · Cataldo Abaterusso[6] · Alessandra A. Mele[6] · Domenico Santoro[7] · Valeria Canale[7] · Alberto Santoboni[8] · Oliviero Filiberti[9] · Fulvio Fiorini[10] · Carlo Mura[11] · Patrizio Imperiali[12] · Silvio Borrelli[1] · Luigi Russo[13] · Luca De Nicola[1] · Domenico Russo[13]

Published online: 4 August 2017

Minotulo et al, Clin Drug Investig (2017) 37:965–973

Conclusion

"This study provides first-time evidence in daily clinical practice that switching from ESA originators to biosimilars is associated with ***poorer anemia control, despite a significant dosing difference of approximately 40%.*** *This finding is also relevant from an economic point of view and it is important to correctly plan resource allocation."*

How did the authors come to this conclusion?

Isolated observational studies with alternate findings

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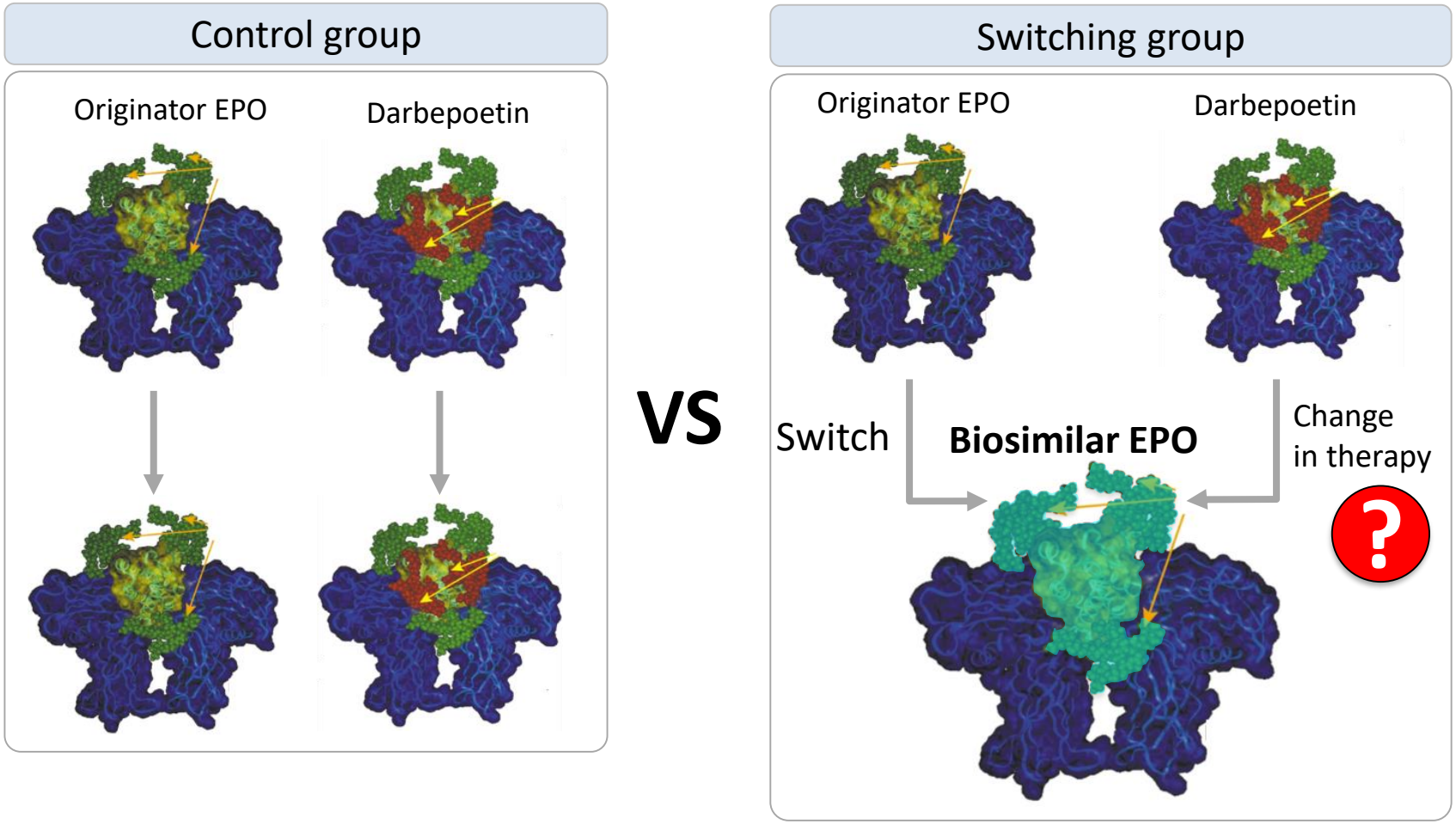

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Changing from darbepoetin is not the same as switching from originator to biosimilar


Clin Drug Investig (2017) 37:965–973
DOI 10.1007/s40261-017-0562-8

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Published online: 4 August 2017
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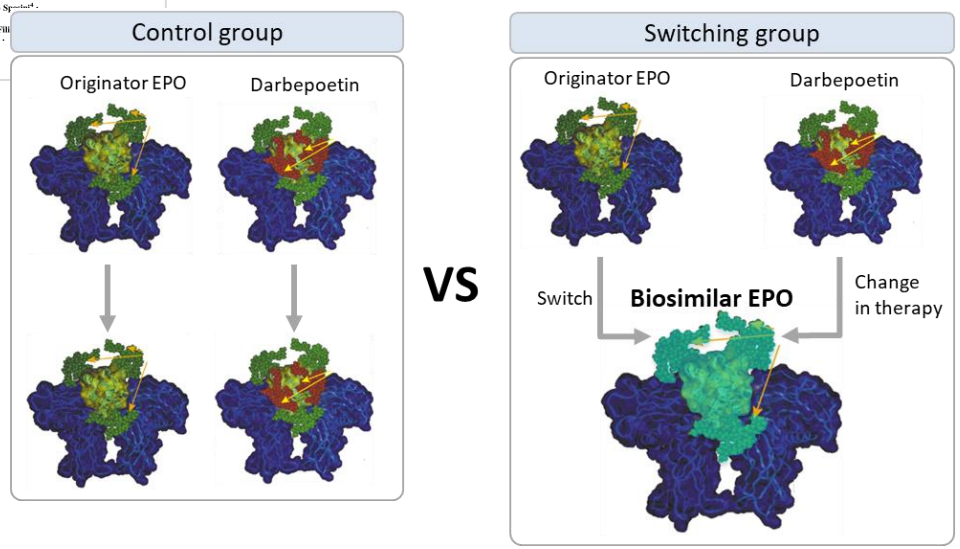
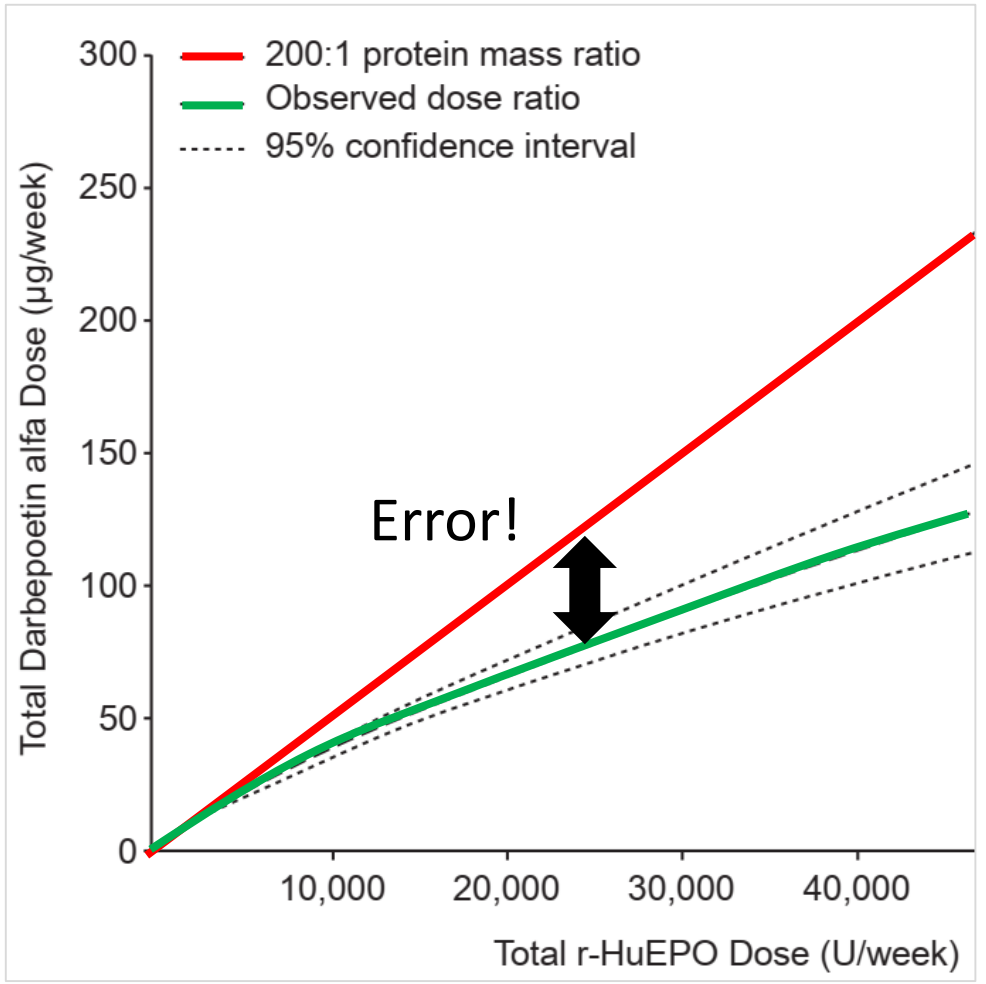
Minotulo et al, Clin Drug Investig (2017) 37:965–973



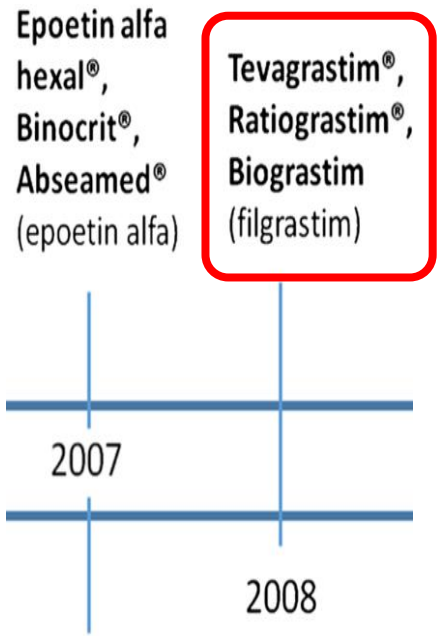
Conclusion

"This study provides first-time evidence in daily clinical practice that switching from ESA originators to biosimilars is associated with ***poorer anemia control, despite a significant dosing difference of approximately 40%.****"*



Scott, Pharmacotherapy. 2002 Sep;22(9 Pt 2):160S-165S.

Biosimilar Filgrastim – real world experience



Support Care Cancer (2017) 25:111–117
DOI 10.1007/s00520-016-3390-0

ORIGINAL ARTICLE

Recombinant granulocyte colony-stimulating factor (rG-CSF) in the management of neutropenia induced by anthracyclines and ifosfamide in patients with soft tissue sarcomas (NEUSAR)

Alberto Bongiovanni[1] · Manuela Monti[2] · Flavia Foca[3] · Federica Recine[1] · Nada Riva[1] · Valentina Di Iorio[3] · Chiara Liverani[1] · Alessandro De Vita[1] · Giacomo Miserocchi[1] · Laura Mercatali[1] · Dino Amadori[1] · Toni Ibrahim[1]

Outcomes for approved indication

"No differences in terms of clinical outcome were seen in patients treated with either biosimilar or originator as prophylaxis for neutropenia induced by EI regimen."

LEUKEMIA & LYMPHOMA, 2018
VOL. 59, NO. 1, 225–228
https://doi.org/10.1080/10428194.2017.1321748
Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Check for updates

Effectiveness of originator (Neupogen) and biosimilar (Zarzio) filgrastim in autologous peripheral blood stem cell mobilization in adults with acute myeloid leukemia: a single-center retrospective study

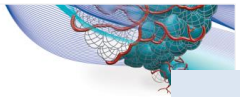
Vincenzo Nasillo[a*], Ambra Paolini[a*], Giovanni Riva[a], Monica Morselli[a], Leonardo Potenza[a], Valeria Coluccio[a], Monica Maccaferri[a], Elisabetta Colaci[a], Valeria Fantuzzi[a], Andrea Messerotti[a], Laura Arletti[a], Valeria Pioli[a], Elisabetta Lugli[a], Andrea Gilioli[a], Chiara Quadrelli[a], Patrizia Zucchini[a], Daniela Vallerini[a], Ivana Lagreca[a], Patrizia Barozzi[a], Angela Cuoghi[a], Paola Bresciani[a], Roberto Marasca[a], Maria Teresa Mariano[b], Giovanni Ceccherelli[b], Patrizia Comoli[c], Daniele Campioli[d], Tommaso Trenti[d], Franco Narni[a], Mario Luppi[a*] and Fabio Forghieri[a*]

[a]Department of Medical and Surgical Sciences, Section of Hematology, University of Modena and Reggio Emilia, Azienda Ospedaliero Universitaria Policlinico, Modena, Italy; [b]Immuno-Transfusional Medicine Unit, Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy; [c]Pediatric Hematology Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Pavia, Italy; [d]Department of Laboratory Medicine and Pathology, Unità Sanitaria Locale (USL), Modena, Italy

Extrapolation of indication

"our findings indicated no difference in key parameters of PBSC mobilization in adult patients affected with AML, with the use of a biosimilar filgrastim, compared with originator, as previously shown for other hematologic malignancies"

Chemotherapy-induced neutropenia/febrile neutropenia prophylaxis with biosimilar filgrastim in solid tumors versus hematological malignancies: MONITOR-GCSF study



Heinz Ludwig[1], Carsten Bokemeyer[2], Matti Aapro[3], Mario Boccadoro[4], Pere Gascón[5], Kris Denhaerynck[6,7], Andriy Krendyukov[8], Ivo Abraham[*,6,9,10,11] & Karen MacDonald[6]
[1]Medizinische Abteilung I – Onkologie und Haematologie, Wilhelminenspital, Wienpäoh, Montleartstraße 37, 1160 Vienna, Austria

Future Oncol. (2019) 15(8), 897–907

Issues of practice

How filgrastim is used not biosimilar vs originator

Biosimilar Filgrastim

Isolated observational studies with alternate findings

LEUKEMIA & LYMPHOMA, 2017
VOL. 58, NO. 9, 2258–2260
http://dx.doi.org/10.1080/10428194.2017.1285025

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Biosimilars of filgrastim in autologous stem cell transplantation: certain differences for myeloma patients only

Christophe Nicol[a]*, Chloé Henry[b]*, Marie-Anne Couturier[a], Pascal Delépine[c], Céline Trip
Caroline Buors[d], Gaëlle Guillerm[a], Christian Berthou[a], Adrian Tempescul[a] and Jean-Chris

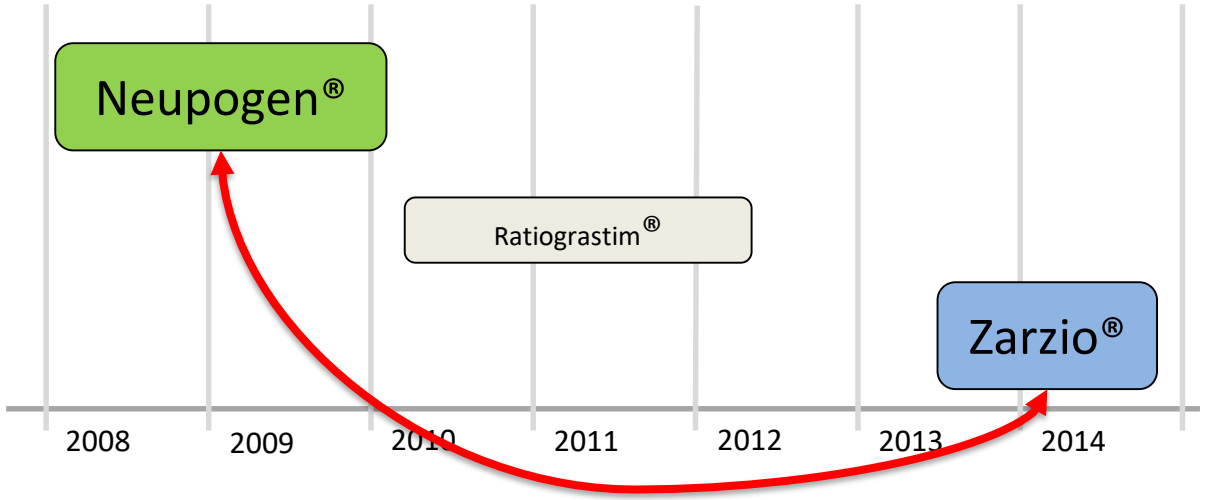
[a]Service d'Hématologie, Institut de Cancéro-Hématologie, Hôpital Morvan, CHRU de Brest, Brest Cedex, France
d'Onco-Pédiatrie, Hôpital Morvan, CHRU de Brest, Brest Cedex, France; [c]Etablissement Français du Sang, Site
Brest Cedex, France; [d]Laboratoire d'Hématologie, Hôpital de la Cavale Blanche, CHRU de Brest, Brest Cedex, F

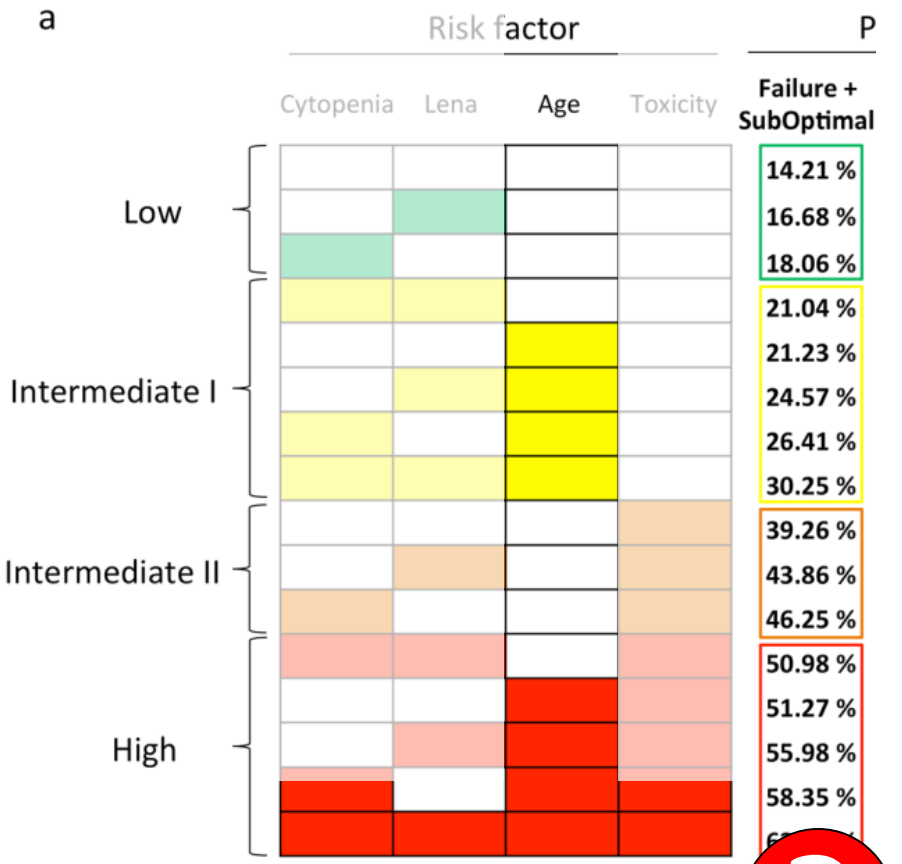
Nicol et al, Leuk Lymphoma. 2017 Sep;58(9):1-3

"We only observed differences on the following studied parameters in the myeloma group: duration of cytopenia, platelet requirements, and bone pain. ***Neupogen®*** *seems to be the most efficient for reducing cytopenia in patients with myeloma (no difference in lymphoma group). In contrast,* ***Zarzio®*** *induced less bone pain and reduced the requirement for platelet units in this same group. The differences observed between the three rhuGCSFs are intriguing.* ***As the procedure was identical through the years, we can therefore assume that they do not have the same intrinsic quality****."*

Use of historic controls

Impact of changes in practice over time





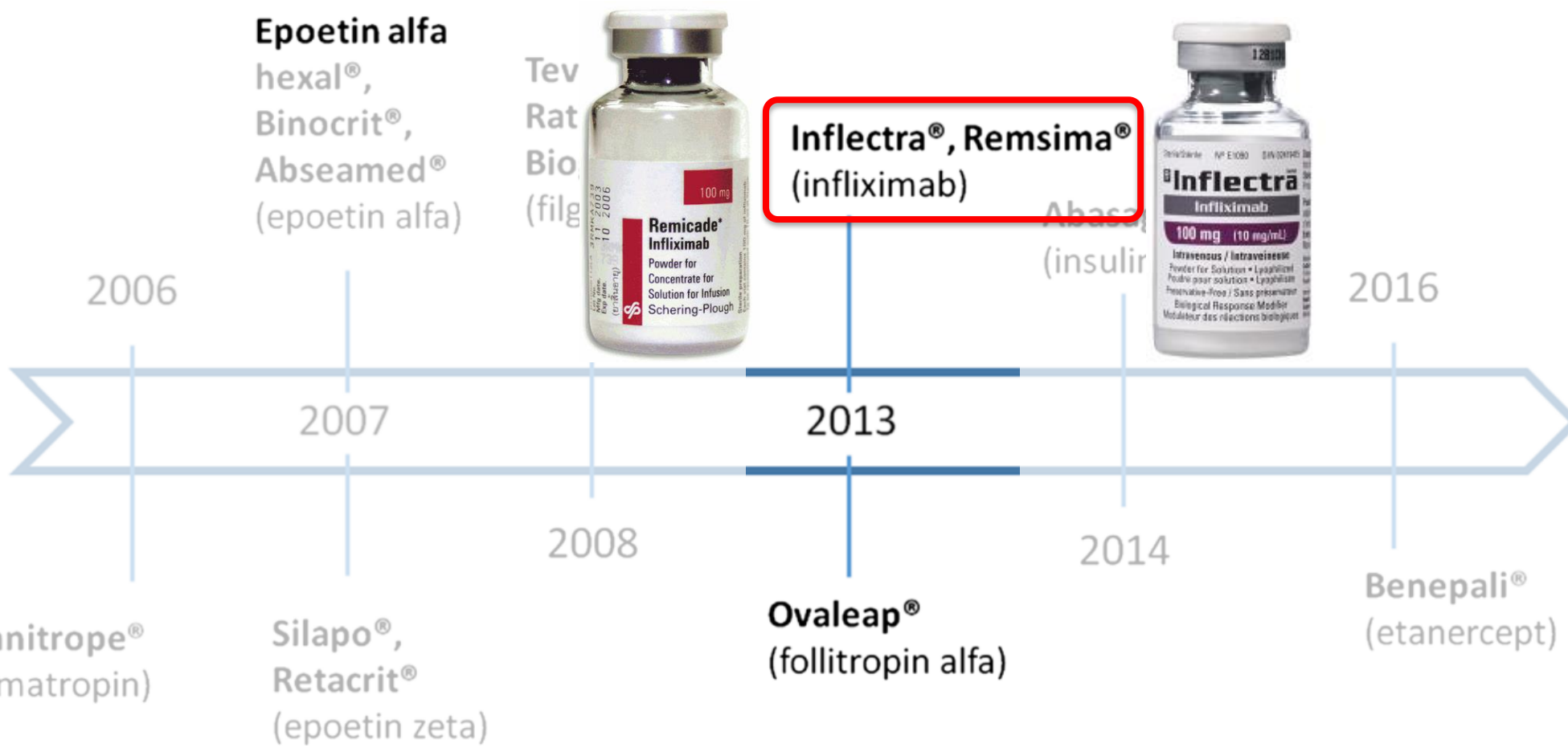
Musto et al. Stem Cell Research & Therapy (2015) 6:64

*"In each group, **patients receiving Zarzio® were also older**, perhaps because the age limit for performing ASCT at our institution has increased through the years (**the patients in the Z-group are the oldest**)."*

Nicol et al, Leuk Lymphoma. 2017 Sep;58(9):1-3

*"As the procedure was identical through the years, **we can therefore assume that they do not have the same intrinsic quality**."*

Global Biosimilar Approval Timeline



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Araújo et al, Curr Rheumatol Rep (2016) 18: 50

Biosimilar Infliximab – real world experience

Multi-centre reports with larger patient numbers

ARD Online First, published on May 4, 2017 as 10.1136/annrheumdis-2016-210742
Clinical and epidemiological research

CONCISE REPORT

A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry

Bente Glintborg,[1,2] Inge Juul Sørensen,[3,4] Anne Gitte Loft,[5] Hanne Lindegaard,[6] Asta Linauskas,[7] Oliver Hendricks,[8] Inger Marie Jensen Hansen,[9] Dorte Vendelbo Jensen,[2,3] Natalia Manilo,[10] Jakob Espesen,[11] Mette Klarlund,[12] Jolanta Grydehøj,[13] Sabine Sparre Dieperink,[3] Salome Kristensen,[14] Jimmi Sloth Olsen,[15] Henrik Nordin,[16] Stavros Chrysidis,[17] Dorte Dalsgaard Pedersen,[18] Michael Veedfald Sørensen,[19] Lis Smedegaard Andersen,[20] Kathrine Lederballe Grøn,[3] Niels Steen Krogh,[21] Lars Pedersen,[22] Merete Lund Hetland,[1,4] On behalf of all departments of rheumatology in Denmark

Conclusion

*"In 802 arthritis patients treated with INX for median >6 years, a nationwide non-medical **switch to CT-P13 had no negative impact on disease activity**. Adjusted 1-year CT-P13 retention rate was slightly lower than for INX in a historic cohort."*

ORIGINAL ARTICLE Inflamm Bowel Dis 2017;23:233–243

The PROSIT-BIO Cohort: A Prospective Observational Study of Patients with Inflammatory Bowel Disease Treated with Infliximab Biosimilar

Gionata Fiorino, MD,[1] Natalia Manetti, MD,[2] Alessandro Armuzzi, MD,[3] Ambrogio Orlando, MD,[4] Angela Variola, MD,[5] Stefanos Bonovas, MD, PhD,[1] Fabrizio Bossa, MD,[6] Giovanni Maconi, MD,[7] Renata D'Incà, MD,[8] Paolo Lionetti, MD,[9] Laura Cantoro, MD,[10] Walter Fries, MD,[11] Maria L. Annunziata, MD,[12] Francesco Costa, MD,[13] Maria M. Terpin, MD,[14] Livia Biancone, MD, Claudio C. Cortelezzi, MD,[16] Arnaldo Amato, MD,[17] Sandro Ardizzone, MD,[18] Silvio Danese, MD,[1] Luisa Guidi, MD,[3] Giulia Rizzuto, MD,[4] Arianna Massella, MD,[5] Angelo Andriulli, MD,[6] Alessandro Massari, MD,[7] Greta Lorenzon, MSN,[8] Silvia Ghione, MD,[9] Anna Kohn, MD,[10] Agostino Ventra, MD,[11] and Vito Annese, MD,[2] The PROSIT-BIO Cohort

Conclusion

*"In summary, in our study with the largest cohort of patients with IBD treated with CT-P13 described so far, we have demonstrated in the evaluated time frame that **the safety profile and efficacy of CT-P13 biosimilar is in line with the existing literature of infliximab**. **No alarming signals of immunization** have been detected in patients switched from the infliximab."*

Research letter British Journal of Dermatology (2017) 177, ppe325–e326

Infliximab biosimilar CT-P13 in the treatment of chronic plaque psoriasis: data from the Psobiosimilars registry

DOI: 10.1111/bjd.15659

DEAR EDITOR, Infliximab is a chimeric human–murine mono-

Conclusion

*"The principal finding of this study is that patients with chronic plaque psoriasis who respond to the infliximab originator can be **switched to the biosimilar CT-P13 without experiencing a significant change in clinical response** or additional adverse events including infusion reactions. Moreover, **CT-P13 is effective also in naïve patients** with a PASI reduction being in line with that reported for the originator. In terms of **safety**, a limited number of adverse events including infusion reactions like those expected with the originator and **without any significant difference between the switch and naïve group** was observed."*

Biosimilar Infliximab

Studies that describe a challenging journey of implementation

Journal of Neurology
https://doi.org/10.1007/s00415-019-09234-y

ORIGINAL COMMUNICATION

Infliximab biosimilar for treating neurosarcoidosis: tolerance and efficacy in a retrospective study including switch from the originator and initiation of treatment

Quentin Riller[1] · Camille Cotteret[2] · Helga Junot[2] · Neila Benameur[2] · Julien Haroche[1] · Alexis Mathian[1] · Miguel Hie[1] · Makoto Miyara[3] · Patrick Tilleul[2] · Zahir Amoura[1] · Fleur Cohen Aubart[1]

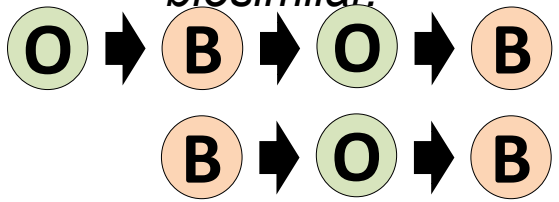
Received: 8 December 2018 / Revised: 27 Jan

Table 1 Clinical characteristics of patients who received the infliximab biosimilar

Patient	Sex, age	Clinical manifestations	Follow-up	S/I	Outcomes[a]	Relapses[b]	Side effects	Prior treatment	Concomitant treatment[c]
#1	F, 41	T, J (M, C, R)	27	I	CR	0	Pulmonary infection	MTX, GC	MTX, GC (5)
#2	F, 37	T, E, S (M, Med)	24	S	PR	0	0	MTX, CYC, AZA, GC	MTX, GC (10)
#3	M, 31	T, E, (C, Med, E)	28	S	–	1 (5)	Infection Urticaria	GC	MTX, GC (7)
#4	M, 32	T, E, (M, ICH)	26	I	PR	0	Urticaria	MTX, GC	MTX, GC (5)
#5	F, 52	T, E, (M, C, Med)	28	S	–	1 (5)	Larva migrans	CYC, GC	MTX, GC(10)
#6	M, 41	T (M, Med, C)	28	S	CR	0	0	CYC, GC	MTX, GC(5)
#7	F, 50	T, S, (M, Med, CN, R, C)	25	S	CR	0	0	MTX, CYC, MMF, GC	MTX, GC(5)
#8	F, 42	T, (M)	27	S	PR	1 (9)	0	MTX, CYC, GC	MTX, GC (5)
#9	M, 29	T, O, (Med)	24	I	PR	0	0	MTX, GC	GC (5)
#10	F, 47	T, (M, CN, ICH)	24	I	PR	0	0	AZA, GC	GC (5)
#11	M, 52	T, (ICH, M)	27	I	PR	0	0	MTX, GC	MTX, GC (5)
#12	F, 49	T, (Med, CN)	28	S	–	0 (2)	Headache	GC	MTX, GC (5)
#13	M, 42	T, S, (C, E, M)	23	I	PR	0	Pulmonary infection	GC, MTX	MTX, GC (5)
#14	M, 32	T, H, (C, M, Med)	24	I	PR	0	0	GC, MTX, CYC, AZA, MMF	AZA, GC (5)
#15	F, 50	T, (M)	22	I	PR	0	Whitlow	GC	GC (10)
#16	F, 47	Hep, (M, C, Med, ICH)	22	I	PR	1 (3)	0	GC	MTX, GC (10)
#17	M, 43	T, E, B (CN, M, C)	19	I	PR	0	0	GC, MTX	MTX (0)
#18	M, 43	B, (C, E)	27	S	PR	1 (7)	Urticaria	GC, CYC	AZA, GC (5)
#19	M, 42	T, B, J, O, (M)	19	I	PR	1 (15)	Diarrhea, urticaria	GC, MTX, HCQ	MTX, HC (0)
#20	M, 50	T, O, (CN)	25	I	CR	0	0	GC	GC (5)

"During the study period, a steering committee was convened consisting of rheumatologists, pharmacists, and internal medicine practitioners who decided to switch to the infliximab originator in individual cases if they had concerns about safety or efficacy."

"Among the six patients who relapsed, five subsequently received the infliximab originator. Four patients did not improve or relapsed with this switch to the originator, thus they were switched back to the biosimilar."



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Biosimilar Infliximab

Isolated observational studies with alternate findings

EXPERT OPINION ON BIOLOGICAL THERAPY, 2016
VOL. 16, NO. 10, 1311–1312
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Gentileschi et al, Expert Opin Biol Ther. 2016;16(10):1311-2

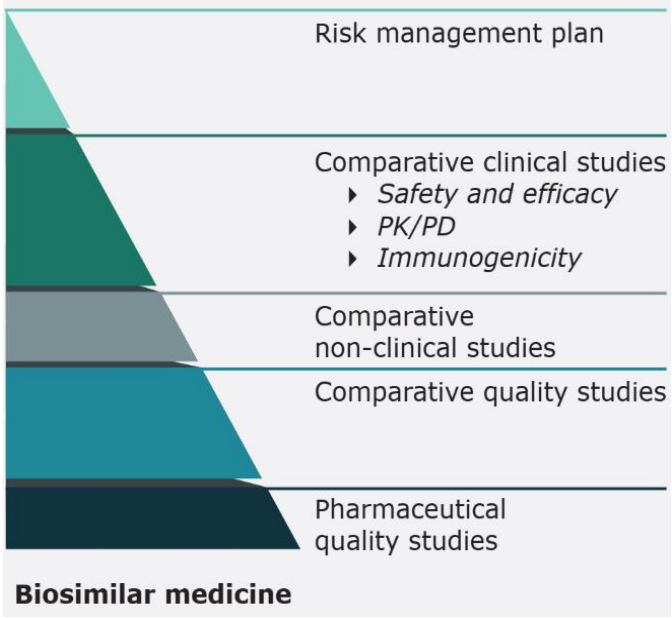
"At the time of the switch, all of the patients were in complete disease remission on INX at a dose of 5 mg/kg every 8 weeks. ***After a mean time of 1.71 months (range 1–2)*** *from the start of INB a* ***disease relapse occurred in 7 out of 23 patients*** *(30.43%). Their mean (SD) duration of previous INX treatment was 62.28 (49.95) months."*

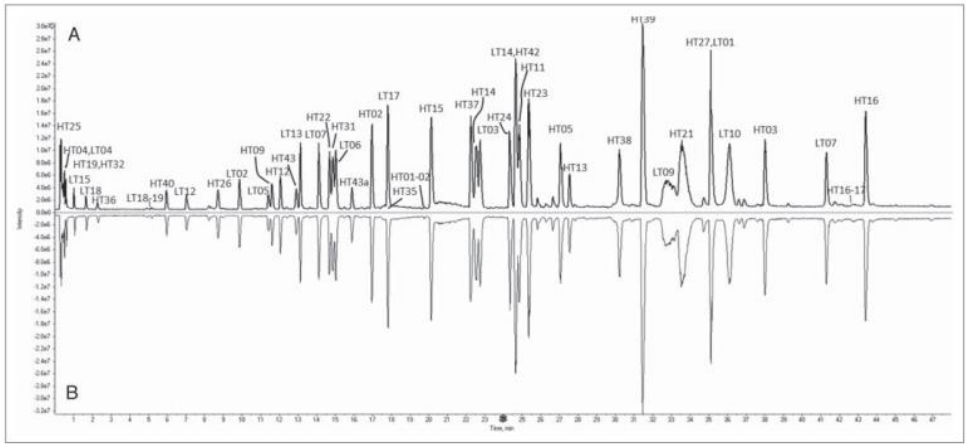
Table 1. Clinical, demographic, and therapeutic characteristics of the refractory patient.

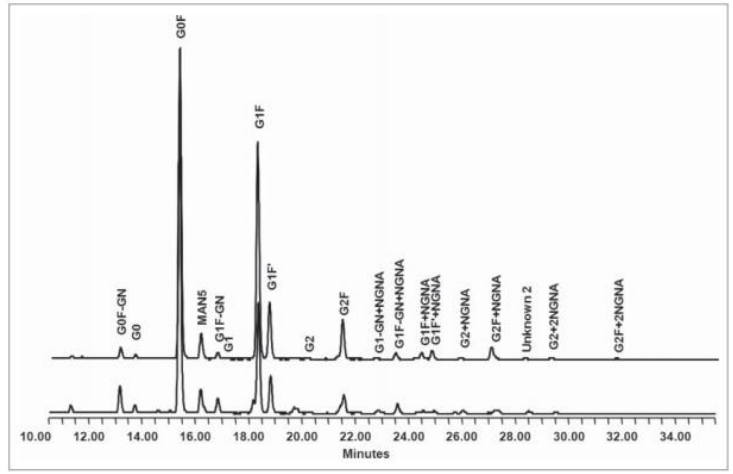
Patient	Age	Gender	HLA B (B27/ B51)	Diagnosis	Concomitant diseases and/or extra-articular manifestations	Age at disease onset	Age at diagnosis	Previous treatments	Duration of previous IFX treatment (months)	Concomitant treatments (during IFX and INB)
1	56	F	–/+	Axial SpA	Behçet's disease	41	51	Etanercept 50 mg/w Adalimumab 40 mg/2w MTX, PDN NSAIDs	20	MTX, NSAIDs
2	23	M	+/–	Axial SpA	Crohn's disease	23	23	NSAIDs SLZ, PDN	3	None
3	49	M	n.k	Axial SpA	None	30	36	NSAIDs, MTX, PDN	63	NSAIDs
4	64	M	+/–	Peripheral SpA	Psoriasis	44	46	NSAIDs, MTX, SLZ, PDN	136	MTX
5	60	F	n.k	Axial SpA	Crohn's disease	46	50	NSAIDs, SLZ, PDN	63	NSAIDs
6	48	M	–/+	Axial SpA	Psoriasis	38	45	NSAIDs, Etanercept 50 mg/w, PDN	19	MTX
7	41	M	+/–	Axial SpA	Psoriasis	14	28	NSAIDS, MTX	132	NSAIDs

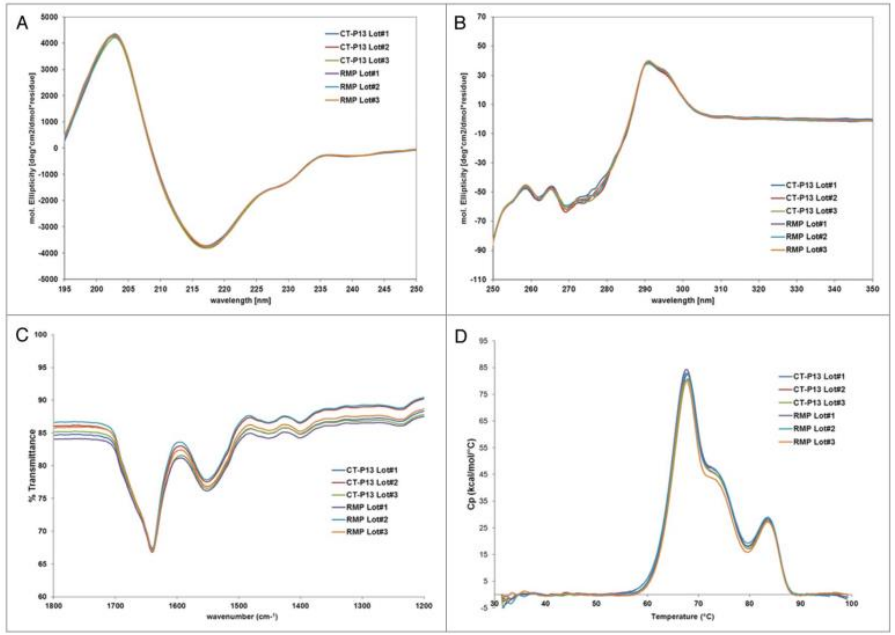
F: female; IFX: infliximab; M: male; MTX: methotrexate; NSAIDs: non-steroidal anti-inflammatory drugs; PDN: prednisone; SLZ: sulphasalazine; W: week; n.k: not known.

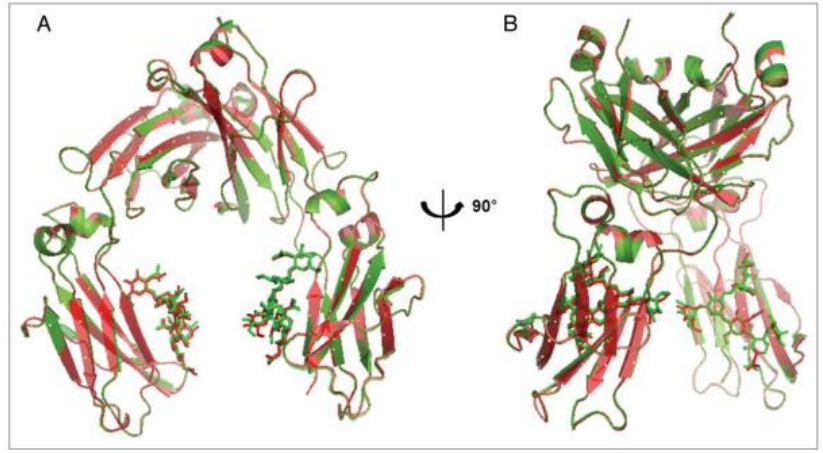
Biosimilar Infliximab











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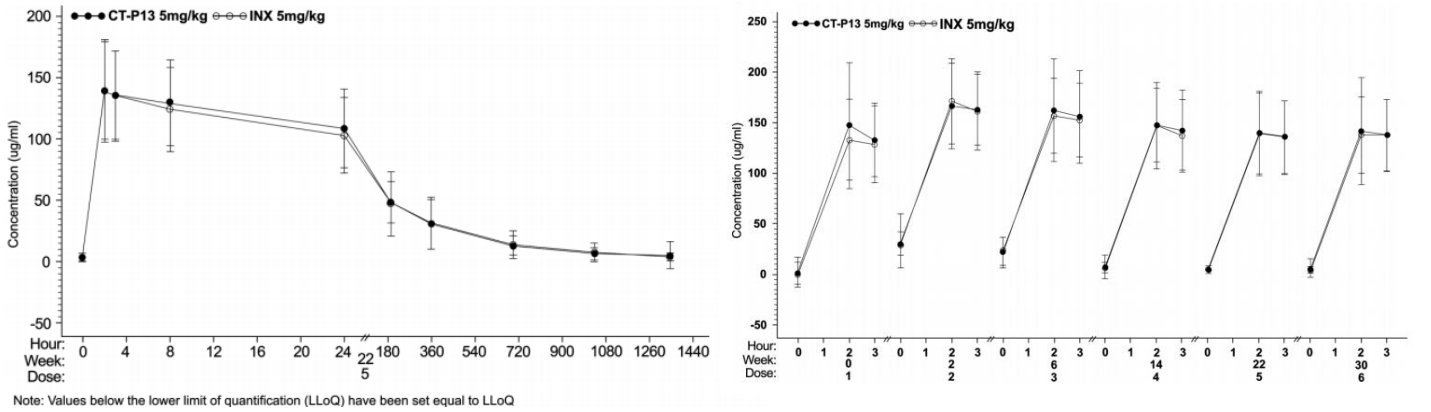
Jung et al. MAbs. 2014 Sep-Oct; 6(5): 1163–1177.

Biosimilar Infliximab

Isolated observational studies with alternate findings

Pharmacokinetics (from PLANETAS study)



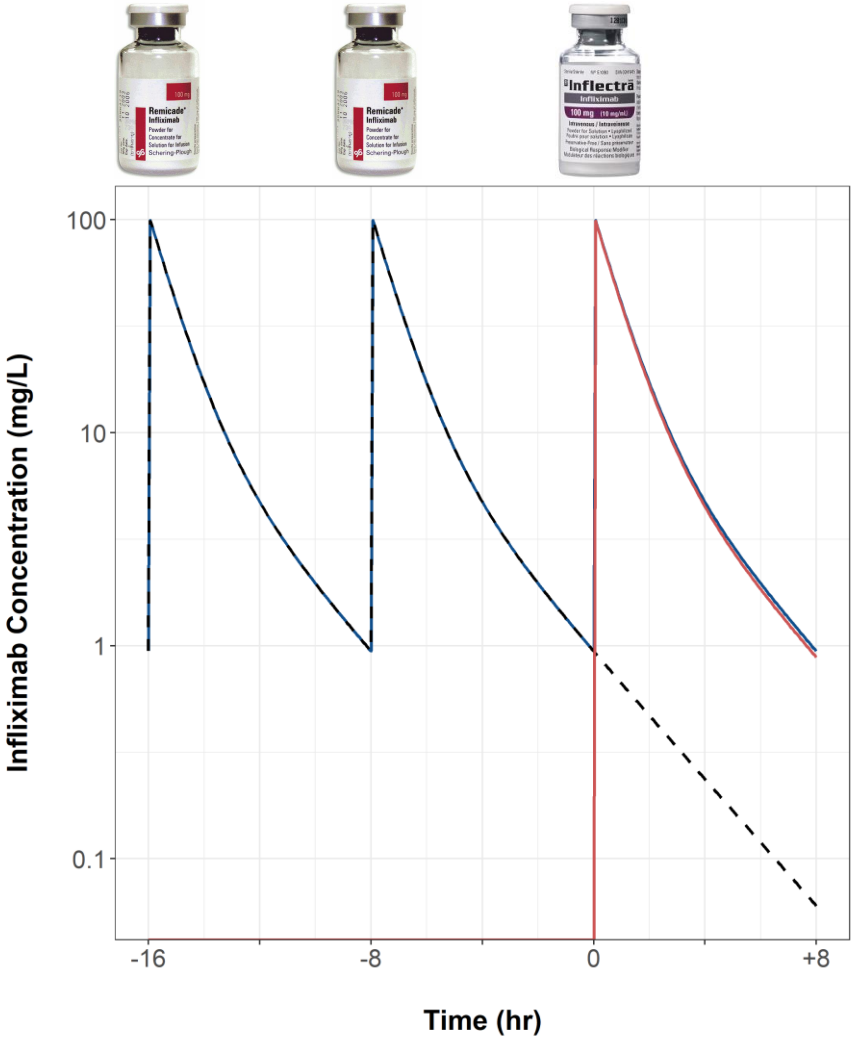
Jung et al. MAbs. 2014 Sep-Oct; 6(5): 1163–1177.

Pharmacodynamics (comparative quality studies)

Table 3. Summary of binding affinity and in vitro potency results

Test items	CT-P13 Average (%) (Range)	SD	RMP Average (%) (Range)	SD	TOST	Method
TNF binding	99 (97–105)	2.5	100 (94–104)	2.8	<0.0001	ELISA
FcRn	101 (95–109)	4.2	97 (93–103)	3.3	<0.0001	SPR
C1q	100 (91–116)	6.6	98 (87–109)	8.2	<0.0001	ELISA
TNF binding	101 (92–110)	6.0	100 (90–112)	7.1	<0.0001	Cell-based
TNF Neutralization	102 (95–107)	4.7	104 (98–110)	2.9	<0.0001	Cell-based
Apoptosis	101 (91–105)	5.0	101 (92–110)	2.5	<0.0001	Cell-based
CDC	102 (91–116)	8.0	93 (84–115)	8.0	0.0011	Cell-based

Park W, Hrycaj P, Jeka S, et al. Ann Rheum Dis 2013;72:1605–1612



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Rheumatology Unit, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy

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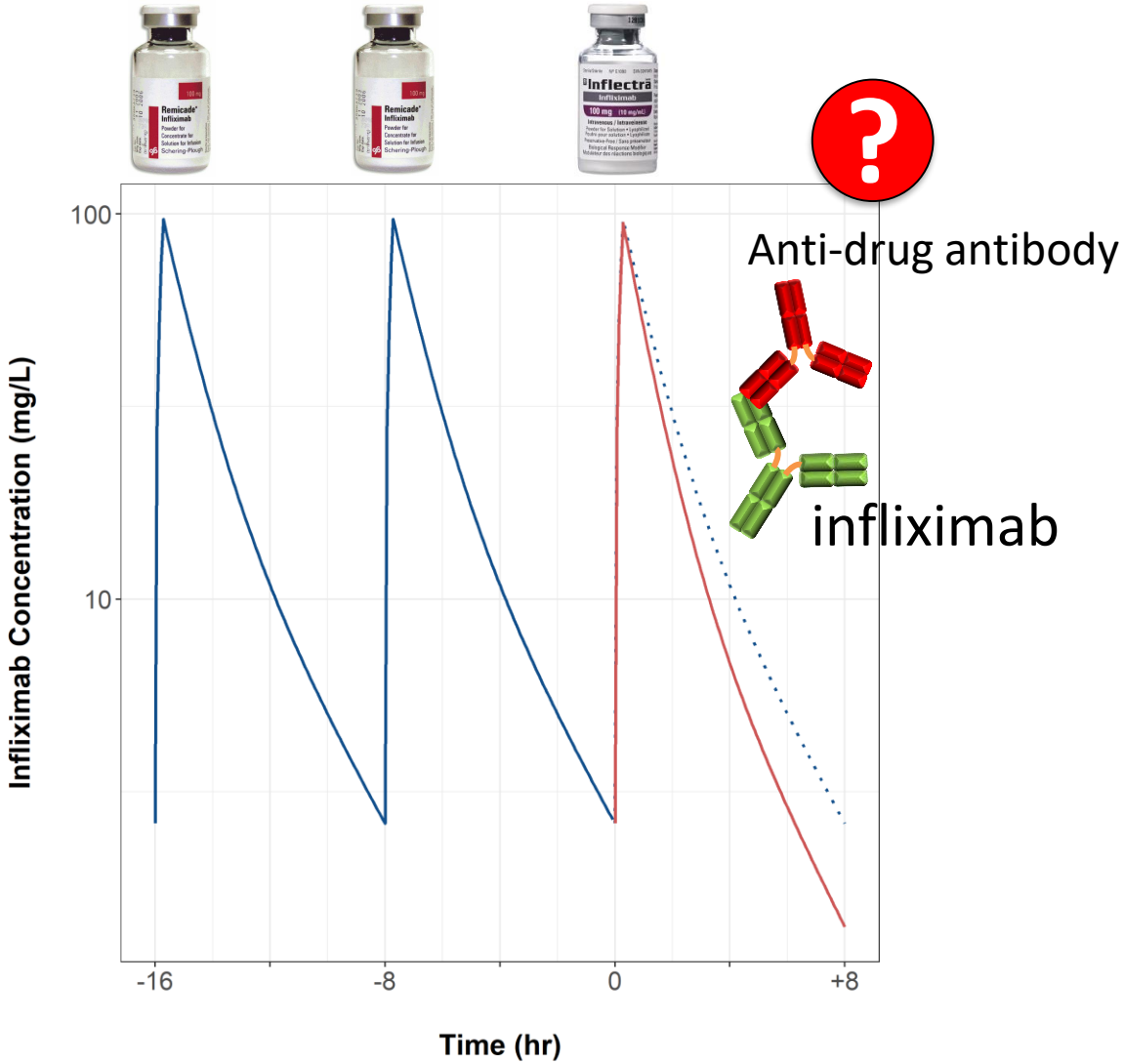

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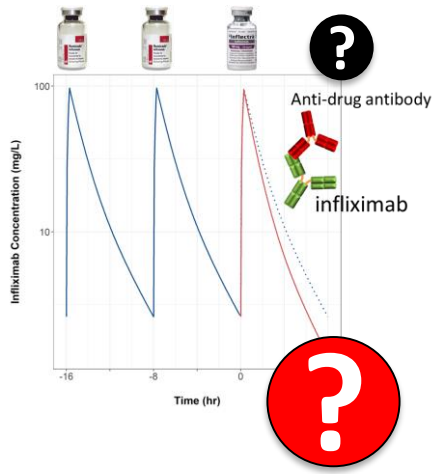


*"INB was then suspended and **IFX was readministered** in all 7 patients at a dose of 5 mg/kg every 8 weeks, in association with a tapering dose of oral corticosteroids. In 5/7, the readministration of INX promptly led to a **remarkable clinical improvement** (4/5), or at least a partial one (1/5), with a significant decrement of the disease activity indexes. No amelioration was observed in 2/7 subjects"*

Biosimilar Infliximab

What do we know about anti-drug antibodies?

BioDrugs (2017) 31:223–237
DOI 10.1007/s40259-017-0219-4

ORIGINAL RESEARCH ARTICLE

Evaluation of the Cross-reactivity of Antidrug Antibodies to CT-P13 and Infliximab Reference Product (Remicade): An Analysis Using Immunoassays Tagged with Both Agents

Walter Reinisch[1,2] · Jørgen Jahnsen[3,4] · Stefan Schreiber[5] · Silvio Danese[6] · Julián Panés[7] · Alejandro Balsa[8] · Won Park[9] · JiSoo Kim[10] · Jee Un Lee[11] · Dae Hyun Yoo[12]

BioDrugs. 2017 Jun;31(3):223-237.

PLOS ONE

RESEARCH ARTICLE

Quantitative comparison of the neutralizing capacity, immunogenicity and cross-reactivity of anti-TNF-α biologicals and an Infliximab-biosimilar

D. J. Buurman[1*], T. Blokzijl[1,2], E. A. M. Festen[1], B. T. Pham[1], K. N. Faber[1], E. Brouwer[3], G. Dijkstra[1]

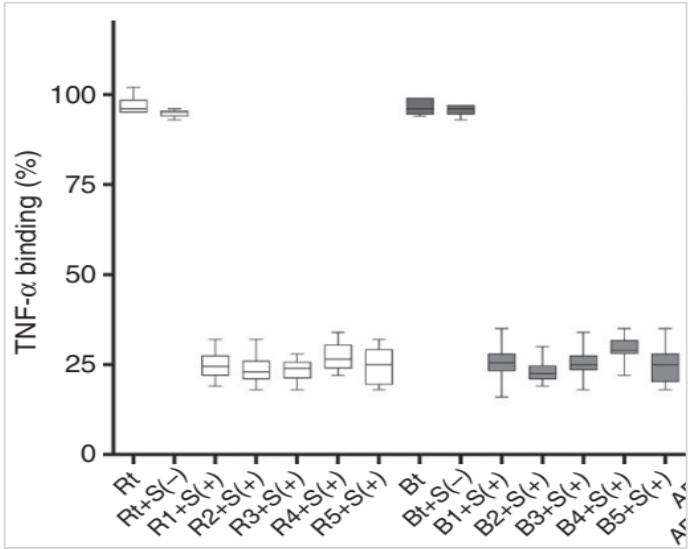
1 Department of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, 2 University of Groningen, University Medical Center Groningen, Department of Laboratory Medicine, Groningen, The Netherlands, 3 Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

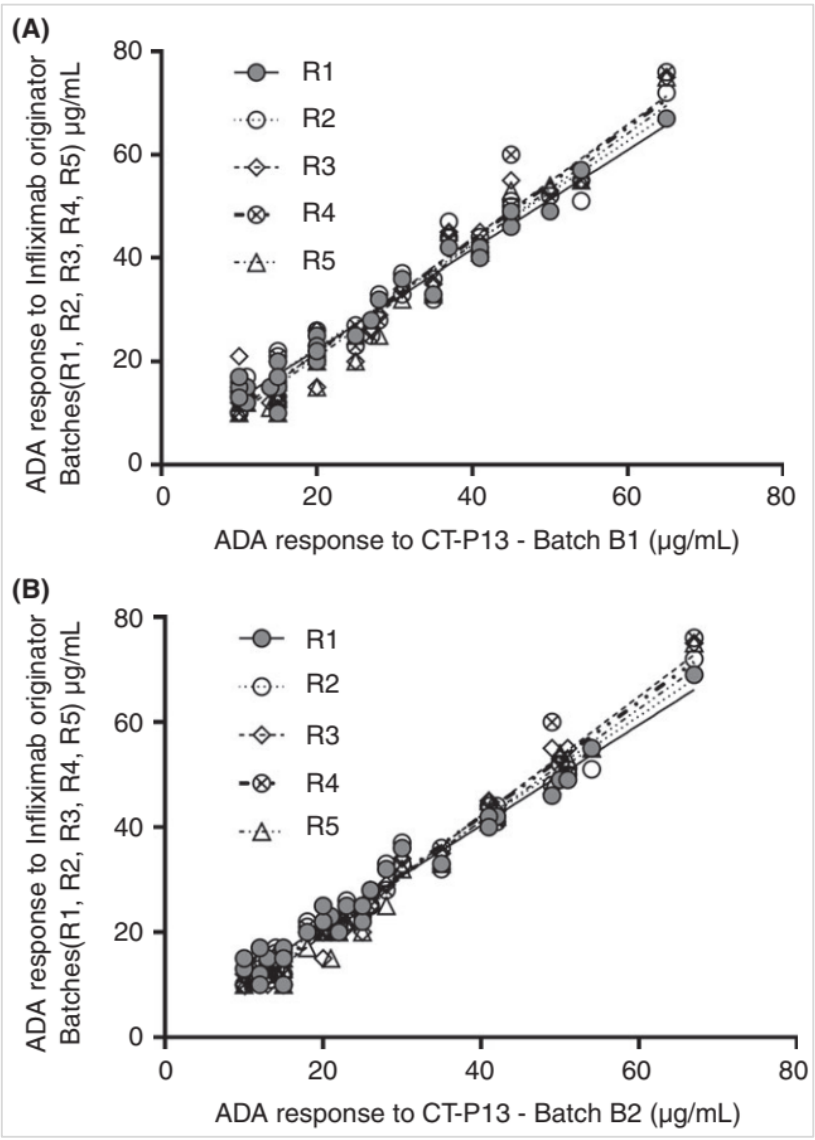
PLoS One. 2018 Dec 11;13(12):e0208922

WILEY Alimentary Pharmacology & Therapeutics

Antigenic response to CT-P13 and infliximab originator in inflammatory bowel disease patients shows similar epitope recognition

J. Goncalves[1] | M. Santos[1] | R. Acurcio[1] | I. Iria[1] | L. Gouveia[1] | P. Matos Brito[1] | A. Catarina Cunha-Santos[1] | A. Barbas[2,3] | J. Galvão[2] | I. Barbosa[2] | F. Aires da Silva[4] | A. Alcobia[5] | M. Cavaco[6] | M. Cardoso[1] | J. Delgado Alves[7,8] | J. J. Carey[9] | T. Dörner[10] | J. Eurico Fonseca[6,11] | C. Palmela[12] | J. Torres[12] | C. Lima Vieira[13] | D. Trabuco[13] | G. Fiorino[14] | A. Strik[15] | M. Yavzori[16] | I. Rosa[17] | L. Correia[18] | F. Magro[19] | G. D'Haens[15] | S. Ben-Horin[16] | P. L. Lakatos[20] | S. Danese[14]





Aliment Pharmacol Ther. 2018 Sep;48(5):507-522.

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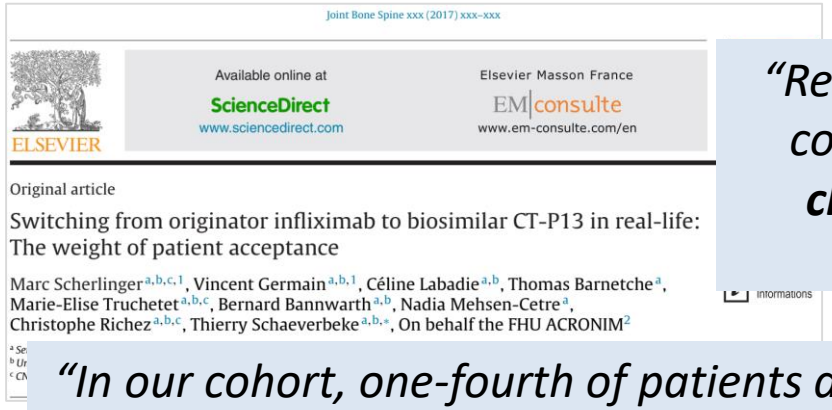
Details of clinical indicators of relapse/response are not provided

Biosimilar Infliximab

Analysing reasons for discontinuation



Joint Bone Spine xxx (2017) xxx–xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

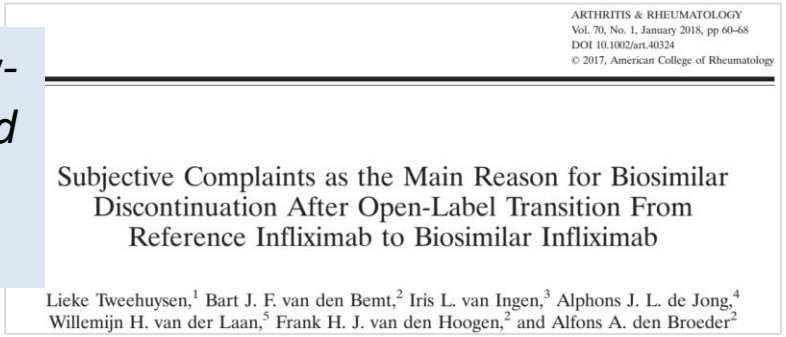
Original article

Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance

Marc Scherlinger[a,b,c,1], Vincent Germain[a,b,1], Céline Labadie[a,b], Thomas Barnetche[a], Marie-Elise Truchetet[a,b,c], Bernard Bannwarth[a,b], Nadia Mehsen-Cetre[a], Christophe Richez[a,b,c], Thierry Schaeverbeke[a,b,*], On behalf the FHU ACRONIM[2]

*"Retention rate was lower after switching from OI to CT-P13 compared to our control cohorts. However, this difference faded after **excluding patients without objective clinical activity**, suggesting a reluctance of patients to the switch and **a negative perception** of the biosimilar."*

*"In our cohort, one-fourth of patients discontinued CT-P13 during 6 months of follow-up, mainly due to an **increase in the subjective features** of the tender joint count and the patient's global assessment of disease activity and/or subjective AEs, **possibly explained by nocebo effects** and/or incorrect causal attribution effects."*



ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 1, January 2018, pp 60–68
DOI 10.1002/art.40324
© 2017, American College of Rheumatology

Subjective Complaints as the Main Reason for Biosimilar Discontinuation After Open-Label Transition From Reference Infliximab to Biosimilar Infliximab

Lieke Tweehuysen,[1] Bart J. F. van den Bemt,[2] Iris L. van Ingen,[3] Alphons J. L. de Jong,[4] Willemijn H. van der Laan,[5] Frank H. J. van den Hoogen,[2] and Alfons A. den Broeder[2]

European Journal of Clinical Pharmacology (2018) 74:655–661
https://doi.org/10.1007/s00228-018-2418-4

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

The nocebo effect challenges the non-medical infliximab switch in practice

N. W. Boone[1] · L. Liu[2] · M. J. Romberg-Camps[2] · L. Duijsens[2] · C. Houwen[1] · P. H. M. va
R. Peeters[4] · R. B. M. Landewé[4,5] · B. Winkens[6] · A. A. van Bodegraven[2]

"….**nocebo response** following a single infusion with infliximab biosimilar. A perceived diminished effect and new-onset headache were reported in these patients."

"…a feeling of less exerted effect, chills during infusions, and numbness of facial skin with tingling limbs were reported in these patients."

Barriers for the uptake of biosimilars

Perceptions are important

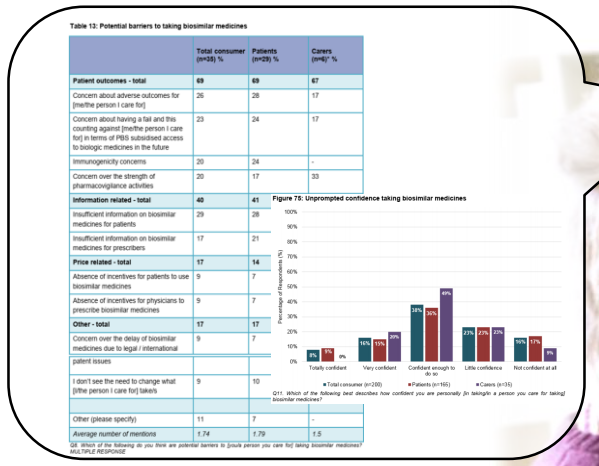


Table 13: Potential barriers to taking biosimilar medicines

	Total consumer (n=35) %	Patients (n=29) %	Carers (n=6)* %
Patient outcomes - total	**69**	**69**	**67**
Concern about adverse outcomes for [me/the person I care for]	26	28	17
Concern about having a fail and this counting against [me/the person I care for] in terms of PBS subsidised access to biologic medicines in the future	23	24	17
Immunogenicity concerns	20	24	-
Concern over the strength of pharmacovigilance activities	20	17	33
Information related - total	**40**	**41**	**17**
Insufficient information on biosimilar medicines for patients	29	28	
Insufficient information on biosimilar medicines for prescribers	17	21	
Price related - total	**17**	**14**	
Absence of incentives for patients to use biosimilar medicines	9	7	
Absence of incentives for physicians to prescribe biosimilar medicines	9	7	
Other - total	**17**	**17**	
Concern over the delay of biosimilar medicines due to legal / international patent issues	9	7	
I don't see the need to change what [I/the person I care for] take/s	9	10	
Other (please specify)	11	7	-
Average number of mentions	*1.74*	*1.79*	*1.5*

Q8. Which of the following do you think are potential barriers to [your/a person you care for] taking biosimilar medicines? MULTIPLE RESPONSE

Figure 78: Unprompted confidence taking biosimilar medicines

Q11. Which of the following best describes how confident you are personally [in taking/in a person you care for taking] biosimilar medicines?

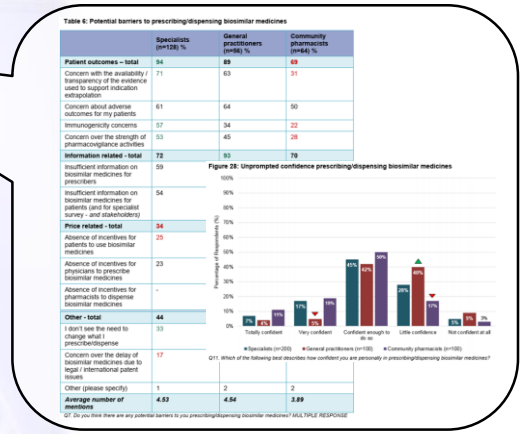


Table 6: Potential barriers to prescribing/dispensing biosimilar medicines

	Specialists (n=128) %	General practitioners (n=66) %	Community pharmacists (n=64) %
Patient outcomes – total	**94**	**89**	**69**
Concern with the availability / transparency of the evidence used to support indication extrapolation	71	63	31
Concern about adverse outcomes for my patients	61	64	50
Immunogenicity concerns	57	34	22
Concern over the strength of pharmacovigilance activities	53	45	28
Information related - total	**72**	**93**	**70**
Insufficient information on biosimilar medicines for prescribers	59		
Insufficient information on biosimilar medicines for patients (and for specialist survey - and stakeholders)	54		
Price related - total	**34**		
Absence of incentives for patients to use biosimilar medicines	25		
Absence of incentives for physicians to prescribe biosimilar medicines	23		
Absence of incentives for pharmacists to dispense biosimilar medicines	-		
Other - total	**44**		
I don't see the need to change what I prescribe/dispense	33		
Concern over the delay of biosimilar medicines due to legal / international patent issues	17		
Other (please specify)	1	2	2
Average number of mentions	*4.53*	*4.54*	*3.89*

Q7. Do you think there are any potential barriers to you prescribing/dispensing biosimilar medicines? MULTIPLE RESPONSE

Figure 23: Unprompted confidence prescribing/dispensing biosimilar medicines

Q11. Which of the following best describes how confident you are personally in prescribing/dispensing biosimilar medicines?

Risk of NOCEBO effect

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Perceptions of biosimilars – Nocebo Effect

Infliximab in patients with rheumatic diseases

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Joint Bone Spine

Original article

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[a] Service de rhumatologie, hôpital Pellegrin, centre hospitalier universitaire de Bordeaux, place Amélie-Raba-Léon, 33076 Bordeaux, France
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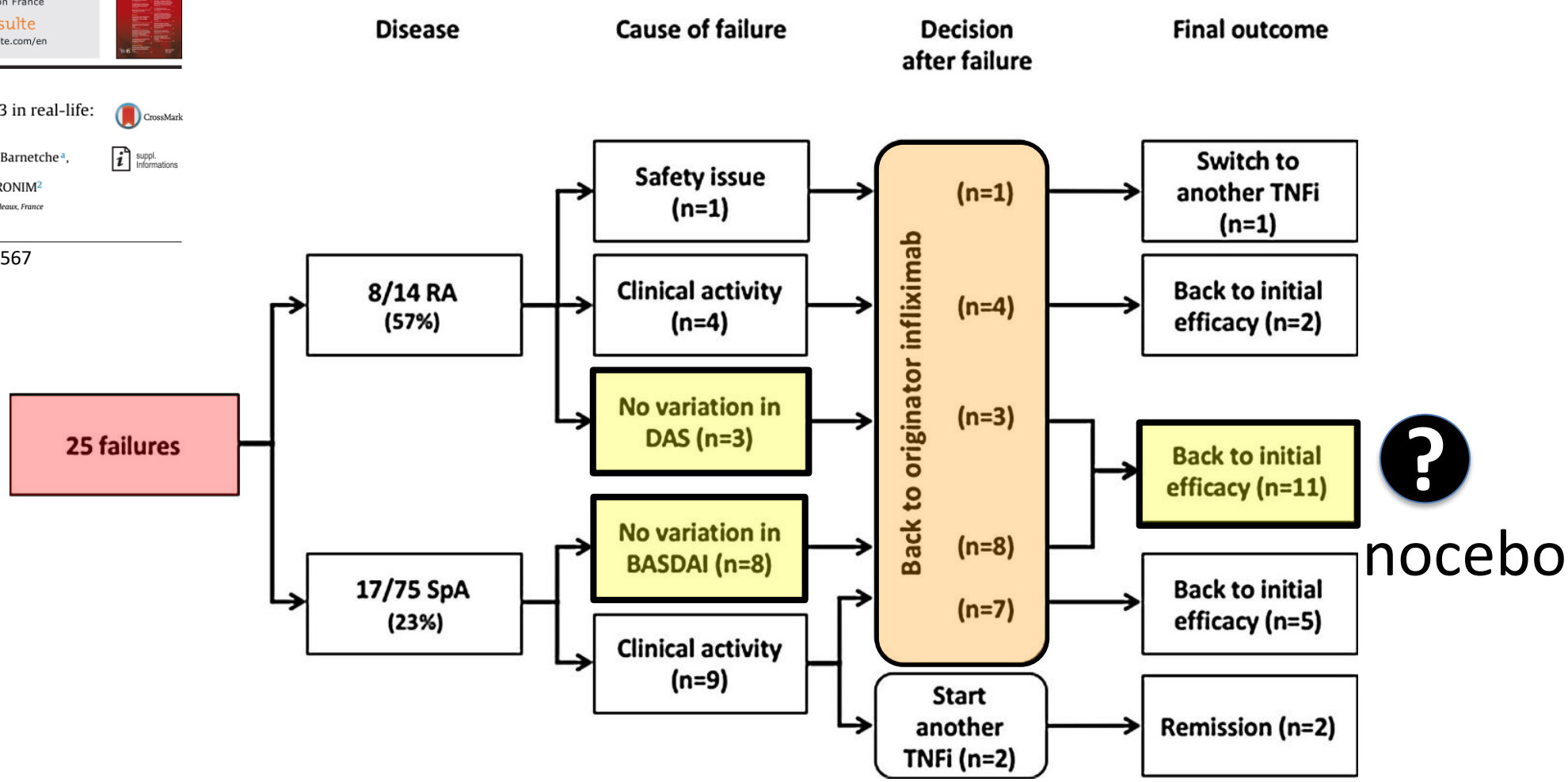
Scherlinger et al, Joint Bone Spine 85 (2018) 561–567

89 patients switched from originator to biosimilar infliximab



?

nocebo

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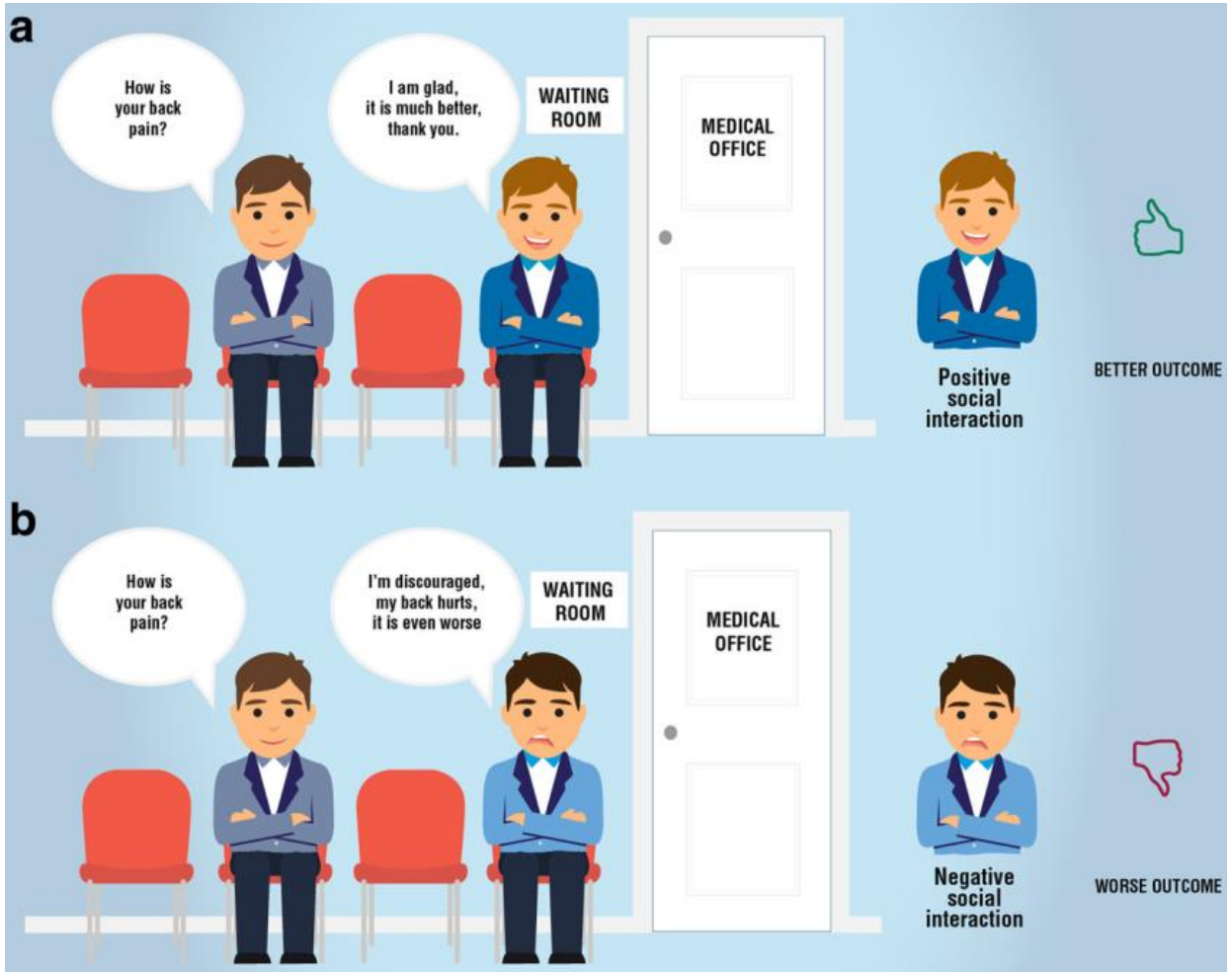
Patient perceptions of biosimilars – Nocebo Effect

Influence of peer beliefs and experiences



Rossettini et al. BMC Musculoskeletal Disorders (2018) 19:27

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Perceptions of Biosimilars – Nocebo Effect

Etanercept in patients with inflammatory arthritis

Clinical and epidemiological research

EXTENDED REPORT

To switch or not to switch: results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry

Bente Glintborg,[1,2] Anne Gitte Loft,[3,4] Emina Omerovic,[5] Oliver Hendricks,[6] Asta Linauskas,[7] Jakob Espesen,[8] Kamilla Danebod,[2] Dorte Vendelbo Jensen,[2] Henrik Nordin,[9] Emil Barner Dalgaard,[10] Stavros Chrysidis,[11] Salome Kristensen,[12] Johnny Lillelund Raun,[13] Hanne Lindegaard,[14] Natalia Manilo,[15] Susanne Højmark Jakobsen,[16] Inger Marie Jensen Hansen,[16] Dorte Dalsgaard Pedersen,[17] Inge Juul Sørensen,[18,19] Lis Smedegaard Andersen,[20] Jolanta Grydehøj,[21] Frank Mehnert,[22] Niels Steen Krogh,[23] Merete Lund Hetland[18,19]

Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2018-213474).

ABSTRACT

Objectives Real-world evidence on effectiveness of switching to biosimila r etanercept is scarce. In Denmark, a nationwide guideline of mandatory switch from 50 mg originator (ETA) to biosimilar (SB4) etanercept was issued for patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA)

Key messages

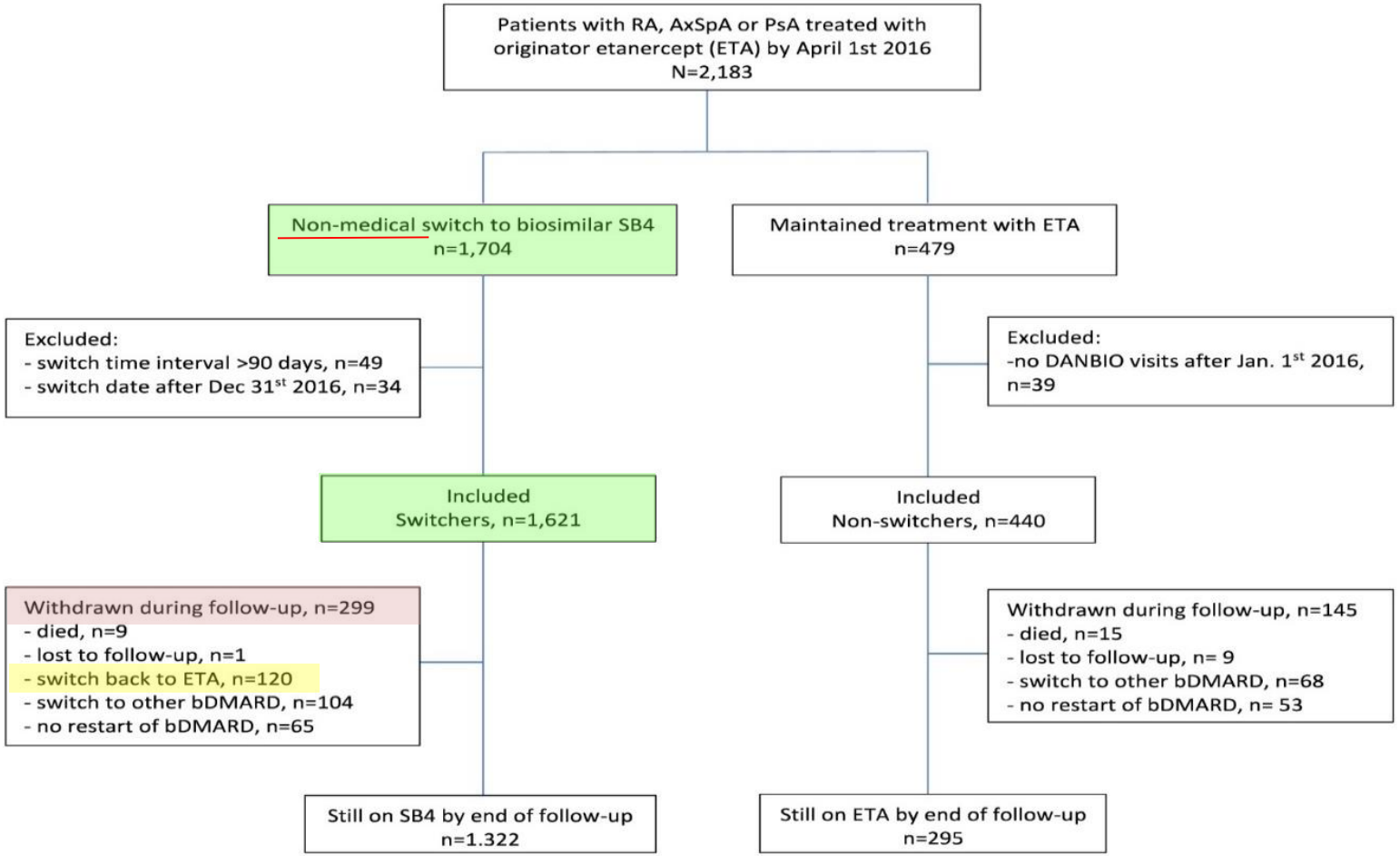
What is already known about this subject?

► Real-world evidence on effectiveness of switching from originator to biosimilar etanercept in inflammatory arthritis is scarce.

Glintborg et al, Ann Rheum Dis. 2018 Nov 5. pii: annrheumdis-2018-213474.

changes in patient global score but not CRP

? nocebo ➡



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Addressing Barriers to Biosimilar Uptake

Managing the Nocebo Effect

Received: 13 December 2018 | First decision: 30 December 2018 | Accepted: 18 February 2019
DOI: 10.1111/apt.15223

WILEY AP&T Alimentary Pharmacology & Therapeutics

Consensus report: clinical recommendations for the prevention and management of the nocebo effect in biosimilar-treated IBD patients

Lieven Pouillon[1,2] | Silvio Danese[3] | Ailsa Hart[4] | Gionata Fiorino[3] | Marjorie Argollo[3,5] | Carlo Selmi[3] | Carmelo Carlo-Stella[3] | Damien Loeuille[1] | Antonio Costanzo[3] | Anthony Lopez[1] | Elena Vegni[3] | Simona Radice[3] | Daniela Gilardi[3] | Marie Socha[1] | Maria Fazio[3] | Marien González-Lorenzo[3] | Stefanos Bonovas[3] | Fernando Magro[6] | Laurent Peyrin-Biroulet[1]

Aliment Pharmacol Ther. 2019 Apr 1. doi: 10.1111/apt.15223. [Epub ahead of print]

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Summary of Consensus Recommendations

The nocebo effect is under-recognised in the era of biosimilars. The nocebo effect can occur when initiating a biosimilar, or when switching to a biosimilar.

Nocebo responses to biosimilars are triggered by a complex interplay of patient-related factors and psychological mechanisms.

When using a biosimilar, caution is needed not to attribute every side effect directly to the treatment, because some side effects may be related to nocebo.

All health-care providers in charge of biosimilar-treated patients need to be aware of the nocebo effect and adopt strategies to minimise it.

Patient-health-care provider relationship is a key driver of acceptance of biosimilars, and limits the risk of negative bias and the nocebo effect.

Lack of knowledge among patients about the effectiveness and safety of biosimilars contributes to the nocebo effect, and should therefore be minimised.

Lack of knowledge and misconceptions among health-care providers about the effectiveness and safety of biosimilars contribute to the nocebo effect, and should therefore be minimised.

Education about biosimilars should be tailored to the individual patient, taking into account their risk profile for the nocebo effect.

Positive framing is recommended to reduce the nocebo effect.

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Perceptions of Biosimilars

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Perceptions of biosimilars

Prescribers and Pharmacists

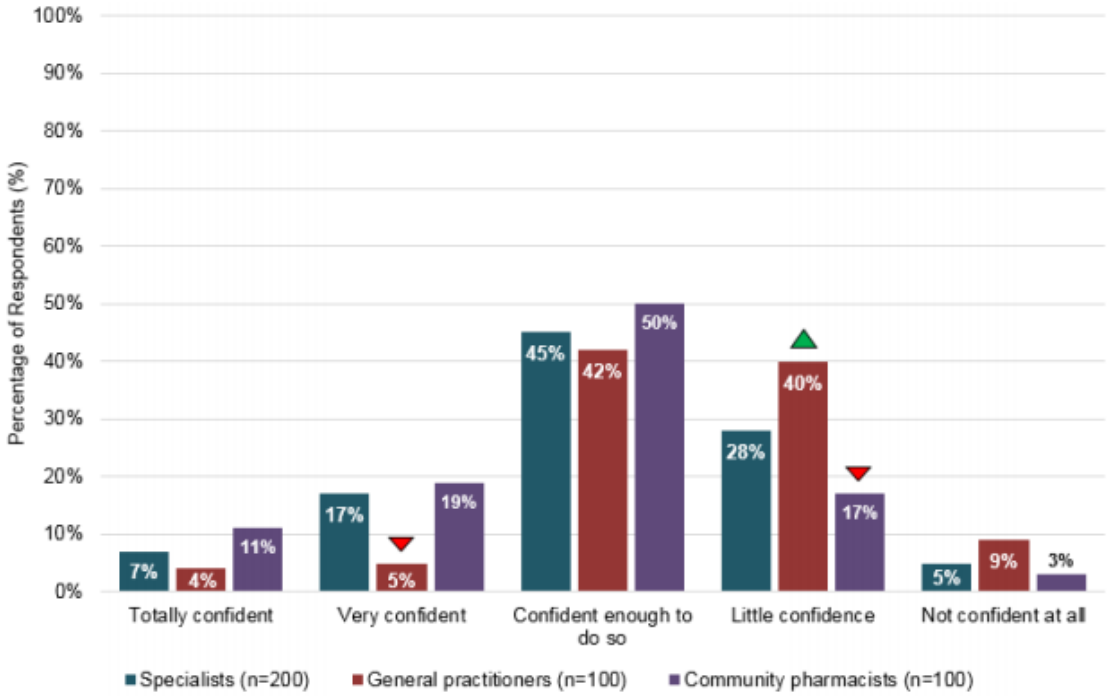
Australian Government
Department of Health

ORC INTERNATIONAL

Market Research for the Pharmaceutical Benefits Schedule (PBS) and Biosimilar Medicines

Quantitative – Report

Figure 28: Unprompted confidence prescribing/dispensing biosimilar medicines



Q11. Which of the following best describes how confident you are personally in prescribing/dispensing biosimilar medicines?

Table 6: Potential barriers to prescribing/dispensing biosimilar medicines

	Specialists (n=128) %	General practitioners (n=56) %	Community pharmacists (n=64) %
Patient outcomes – total	**94**	**89**	**69**
Concern with the availability / transparency of the evidence used to support indication extrapolation	71	63	31
Concern about adverse outcomes for my patients	61	64	50
Immunogenicity concerns	57	34	22
Concern over the strength of pharmacovigilance activities	53	45	28
Information related - total	**72**	**93**	**70**
Insufficient information on biosimilar medicines for prescribers	59	89	50
Insufficient information on biosimilar medicines for patients (and for specialist survey - *and stakeholders)*	54	59	58
Price related - total	**34**	**32**	**69**
Absence of incentives for patients to use biosimilar medicines	25	16	61
Absence of incentives for physicians to prescribe biosimilar medicines	23	27	17
Absence of incentives for pharmacists to dispense biosimilar medicines	-	-	33
Other - total	**44**	**43**	**38**
I don't see the need to change what I prescribe/dispense	33	18	13
Concern over the delay of biosimilar medicines due to legal / international patent issues	17	38	25
Other (please specify)	1	2	2
Average number of mentions	***4.53***	***4.54***	***3.89***

Q7. Do you think there are any potential barriers to you prescribing/dispensing biosimilar medicines? MULTIPLE RESPONSE

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http://www.health.gov.au/internet/main/publishing.nsf/Content/biosimilar-market-research

Perceptions of biosimilars

Consumers

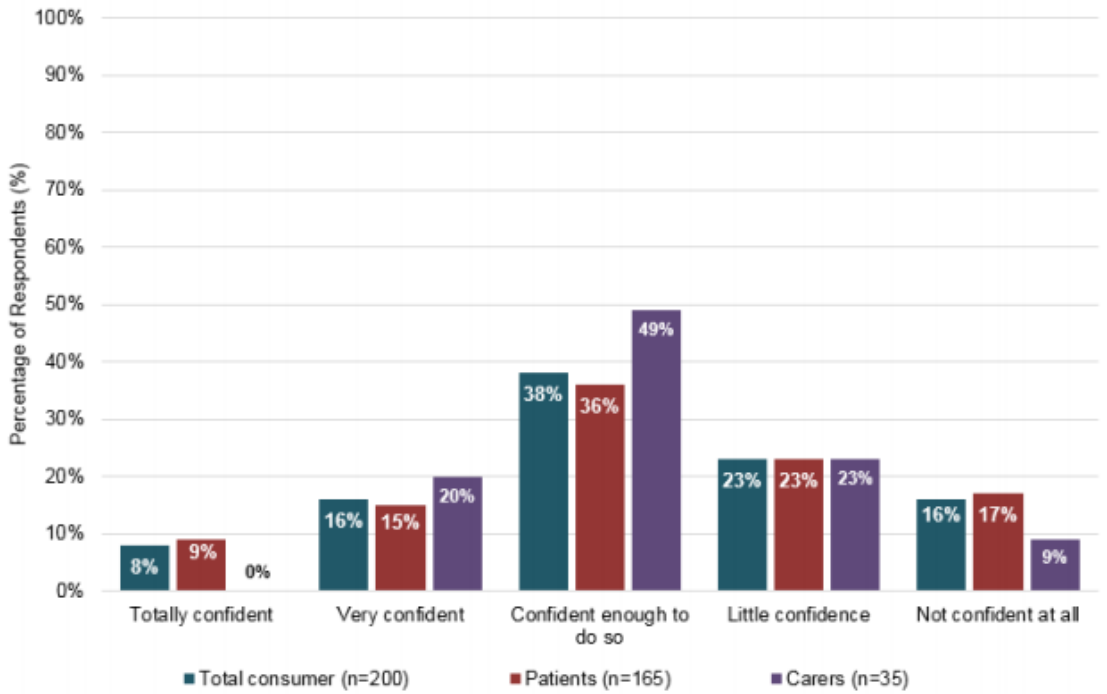
Australian Government
Department of Health

ORC INTERNATIONAL

Market Research for the Pharmaceutical Benefits Schedule (PBS) and Biosimilar Medicines

Quantitative – Report

Figure 75: Unprompted confidence taking biosimilar medicines



Q11. Which of the following best describes how confident you are personally [in taking/in a person you care for taking] biosimilar medicines?

Table 13: Potential barriers to taking biosimilar medicines

	Total consumer (n=35) %	Patients (n=29) %	Carers (n=6)* %
Patient outcomes - total	**69**	**69**	**67**
Concern about adverse outcomes for [me/the person I care for]	26	28	17
Concern about having a fail and this counting against [me/the person I care for] in terms of PBS subsidised access to biologic medicines in the future	23	24	17
Immunogenicity concerns	20	24	-
Concern over the strength of pharmacovigilance activities	20	17	33
Information related - total	**40**	**41**	**33**
Insufficient information on biosimilar medicines for patients	29	28	33
Insufficient information on biosimilar medicines for prescribers	17	21	-
Price related - total	**17**	**14**	**33**
Absence of incentives for patients to use biosimilar medicines	9	7	17
Absence of incentives for physicians to prescribe biosimilar medicines	9	7	17
Other - total	**17**	**17**	**17**
Concern over the delay of biosimilar medicines due to legal / international patent issues	9	7	17
I don't see the need to change what [I/the person I care for] take/s	9	10	-
Other (please specify)	11	7	-
Average number of mentions	*1.74*	*1.79*	*1.5*

Q8. Which of the following do you think are potential barriers to [you/a person you care for] taking biosimilar medicines? MULTIPLE RESPONSE

http://www.health.gov.au/internet/main/publishing.nsf/Content/biosimilar-market-research

Overcoming perceptions

Addressing nocebo through education

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Overcoming perceptions

Prescriber and Pharmacist Education

Australian Government
Department of Health

Biosimilar medicines:
the basics
for health care professionals

- What are biological and biosimilar medicines?
- How are biosimilar medicines developed?
- Who chooses whether the biosimilar medicine is used?
- Is there a difference in health outcomes between the biosimilar medicine and the reference biological medicine?
- How is the safety of biosimilar medicines monitored (pharmacovigilance)?
- Where can I find more information?

What are biological and biosimilar medicines?

Biological medicines, including biosimilar medicines, contain one or more active substances that are derived from living cells or organisms.

These medicines are used to treat serious diseases such as cancers, diabetes, rheumatoid arthritis, severe psoriasis, kidney disease, multiple sclerosis, and inflammatory bowel diseases such as ulcerative colitis and Crohn's disease.

Biosimilar medicines are highly similar, but not identical, versions of an already registered biological medicine (the reference biological medicine). This is because the inherent variability of the biological systems used in the manufacturing process means that the resulting product is also variable. No two batches of a biological medicine, including biosimilar medicines, are ever exactly the same (even from the same manufacturer).

For a biosimilar medicine to be approved, its structural variability must not be greater than the acceptable limits of batch variation for the reference biological medicine. All critical quality attributes (i.e. those important for the function of the molecule) must be highly similar.

Biosimilar medicines that are approved for marketing have been assessed to have no clinically meaningful differences and to be therapeutically equivalent to the reference biological medicine.

Biosimilar medicines are expected to deliver significant savings, which can be reinvested into other areas of the Australian health system and **expand access to biological medicines as they become more affordable**.

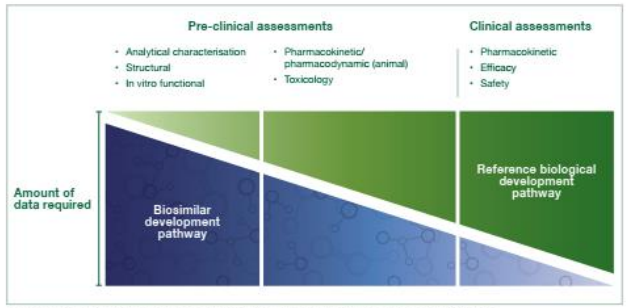
How are biosimilar medicines developed?

The development process varies between reference biological and biosimilar medicines:

- In reference biological medicine development, the majority of time and effort is spent in clinical studies that establish the clinical benefit of the medicine.
- In biosimilar medicine development, the majority of time and effort is spent in comprehensive analytical comparison studies that establish the similarity of the medicine to the reference biological medicine, because the clinical benefits have already been established.

As a result of these studies, it has been **determined that there are no significant differences in the critical quality attributes that affect safety, effectiveness or quality**.

Comparison of the development pathway of reference biological vs biosimilar medicines



Adapted from Bui et al (2015). Key considerations in the preclinical development of biosimilars. *Drug Discovery Today* 20(9):3–15

Who chooses whether the biosimilar medicine is used?

The medicine used for treatment is a choice that is made by doctors in consultation with their patients. Health care professionals are encouraged to talk through these choices with their patients. The *Biosimilar medicines: the basics – information for consumers and carers* brochure is aimed at consumers and will help to answer common questions.

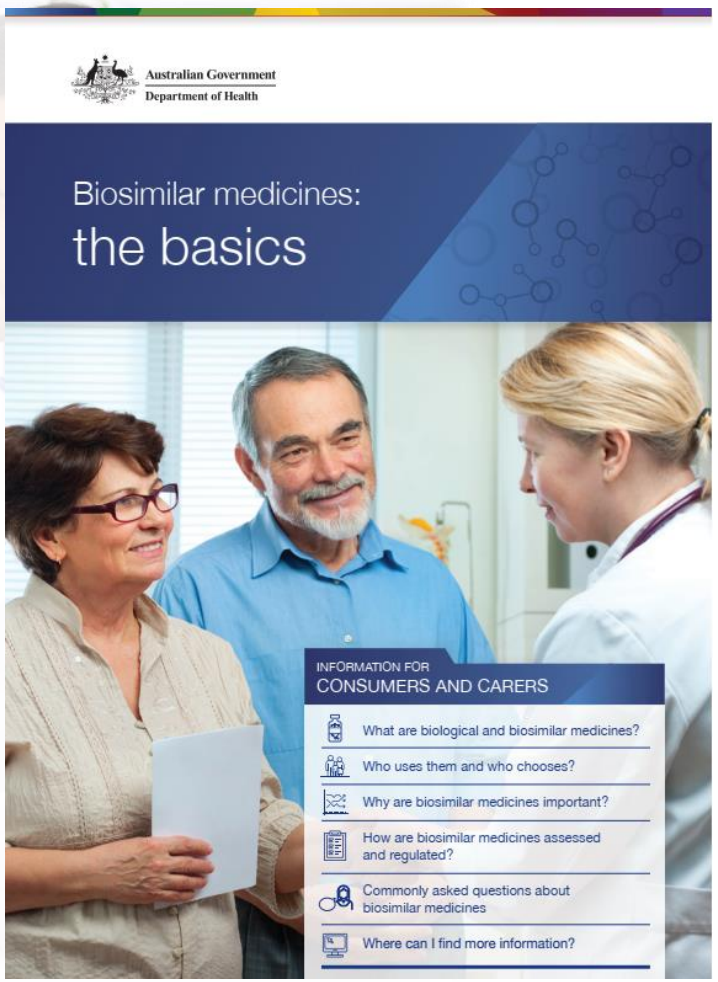
If one brand of medicine can be exchanged for another by the pharmacist, they are 'substitutable', which means pharmacists can substitute between brands in consultation with the patient but without needing to refer back to the doctor. Substitution between brands of biological medicines is considered by the Pharmaceutical Benefits Advisory Committee (PBAC) and recommended on a case-by-case basis.

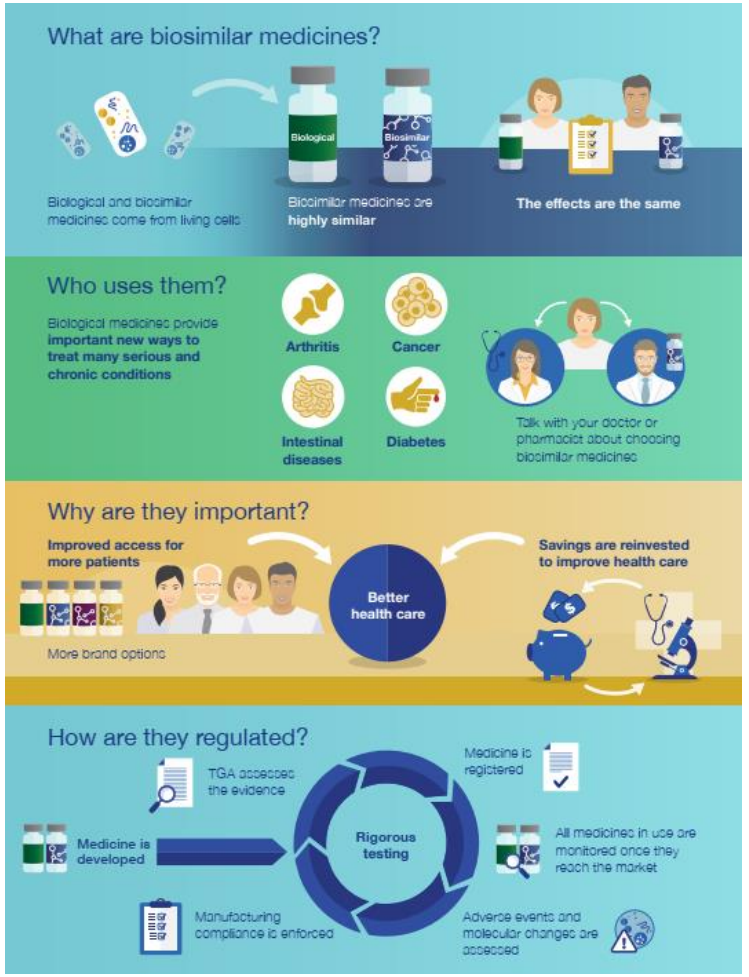
Even if a medicine is substitutable, the doctor can tick the 'brand substitution not permitted' box when writing a prescription. If this box is ticked, by law the pharmacist cannot dispense a brand other than that prescribed.

In the public hospital setting, brand decisions are made by clinician-led committees and are based on the safety, efficacy and cost-effectiveness of the medicine. For more information, refer to the guiding principles from the Council of Australian Therapeutic Advisory Groups on the governance of biological and biosimilar medicines in Australian hospitals (www.catag.org.au/resources/#guidance).

http://www.health.gov.au/internet/main/publishing.nsf/content/biosimilar-awareness-initiative/$File/Biosimilar-medicines-the-basics-for-healthcare-professionals-Brochure.pdf

Overcoming perceptions
Patient Education





http://www.health.gov.au/internet/main/publishing.nsf/content/biosimilar-awareness-initiative/$File/Biosimilar-medicines-the-basics-for-consumers-and-carers-Bochure.pdf

Barriers for the uptake of biosimilars

Overcoming Perceptions

Seminars in Arthritis and Rheumatism 000 (2018) 1–6

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

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

Acceptance rate and sociological factors involved in the switch from originator to biosimilar etanercept (SB4)

Marc Scherlinger[a,b,c,1,*], Emmanuel Langlois[b,c,d,1], Vincent Germain[a,b,1], Thierry Schaeverbeke[a,b,1]

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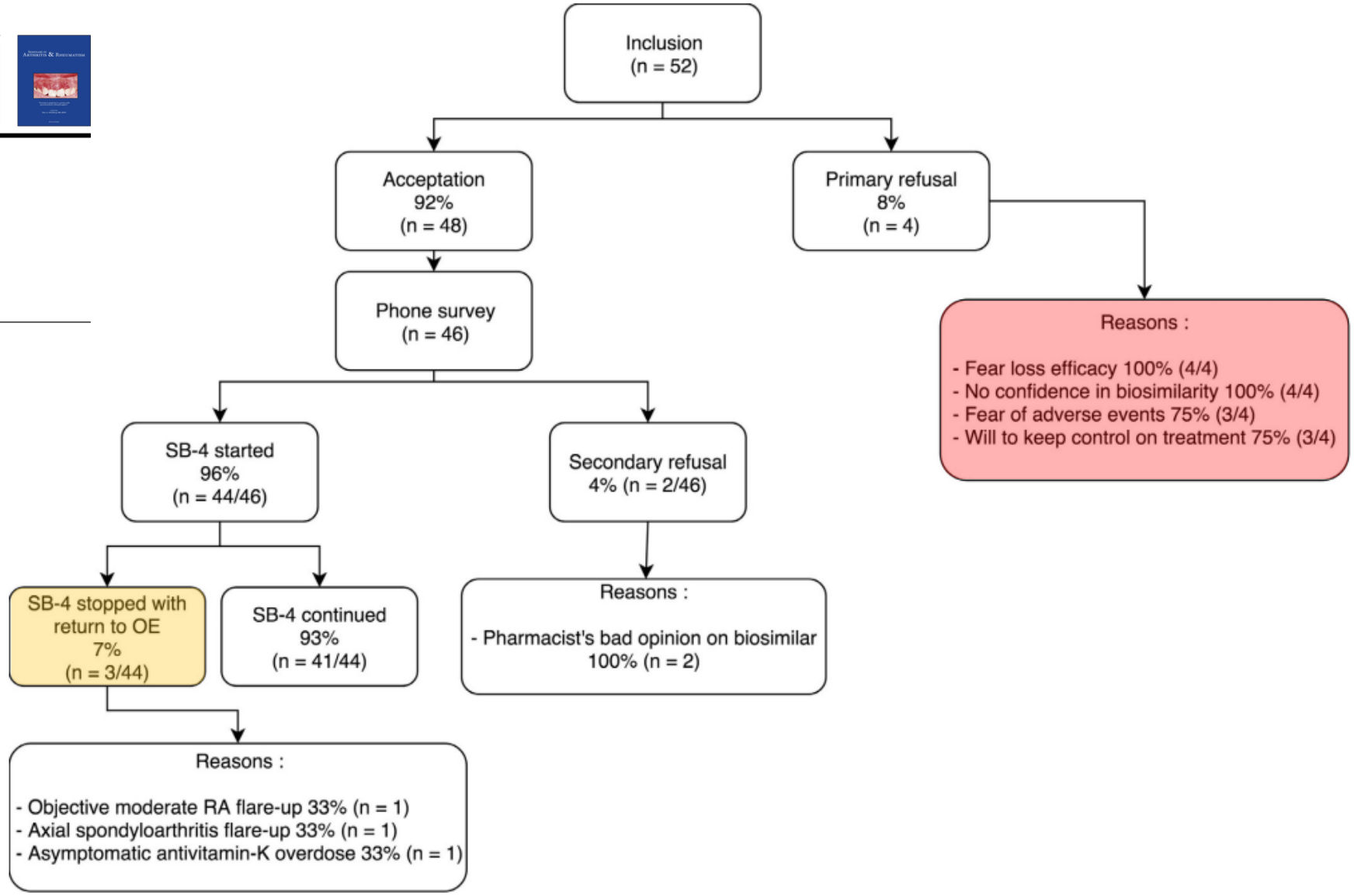
[c] CNRS-UMR 5164 Immuno Concept, 146 rue Léon Saignat, 33076 Bordeaux, France
[d] CNRS-UMR 5516 Centre Emile Durkheim, 11 allée Ausone, 33607 Pessac Cedex France

Semin Arthritis Rheum. 2019 Apr;48(5):927-932



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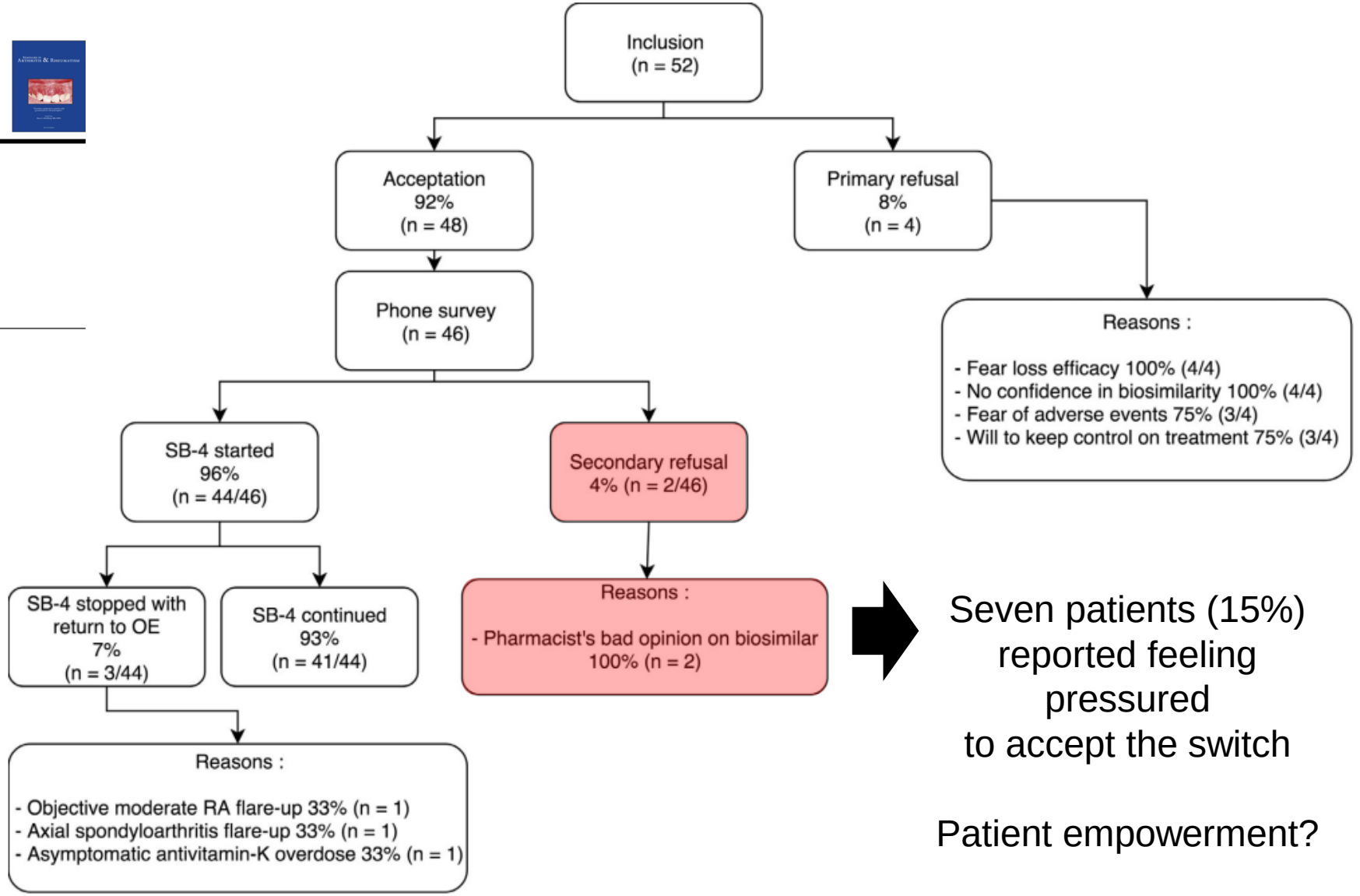

Seven patients (15%) reported feeling pressured to accept the switch

Patient empowerment?

Conclusions

- Biosimilar medicines undergo a rigorous evaluation process prior to approval
- Overall real-world experience with biosimilars supports no difference in safety and efficacy between biosimilar and originator products
  - careful critical review is required of observational studies
- Evidence that immunogenic epitopes and anti-drug antibodies toward infliximab are the same for biosimilar and originator infliximab
- Patient, prescriber and pharmacist perceptions are very important
  - risk of nocebo effect
- Education is critical