PeerCME

Biosimilars for Haematologic Malignancies: The Path to Sustainable Care

The Role of Biosimilars in Promoting Sustainability of Care

Paul Cornes, BA, BM BCH, MA, MRCP, FRCR
Comparative Outcomes Group
Bristol, United Kingdom

A Look at Biosimilars Development

Arnold G. Vulto, PharmD, PhD, FCP
Erasmus University Medical Center
Rotterdam, The Netherlands

The Role of New Molecule Innovation in the Sustainability of Treatment for Haematologic Malignancies

Prof. Wojciech Jurczak, MD, PhD
Jagiellonian University
Krakow, Poland

Ask the Faculty

Paul Cornes, BA, BM BCH, MA, MRCP, FRCR
Arnold G. Vulto, PharmD, PhD, FCP
Prof. Wojciech Jurczak, MD, PhD

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CME Details

Funding Disclosure
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Activity Description and Educational Objectives
In this activity, experts in haematologic malignancies discuss the role of biosimilars in improving sustainability of care in the treatment of these diseases.

Upon completion of this activity, participants should be better able to:
- Recognise the similarities and differences between biosimilars and originators
- Review the role of biosimilars in sustainability of treatment for haematologic malignancies
- Evaluate the data on monoclonal antibodies for the treatment of haematologic malignancies and the role of biosimilar monoclonal antibodies to address some lingering gaps in care

Target Audience
This activity has been designed to meet the educational needs of haematologist-oncologists, haematologists, and pharmacists, as well as other clinicians involved in the management of haematologic malignancies.

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Course Director and Moderator
Paul Cornes, BA, BM BCH, MA, MRCP, FRCR
Oncologist, Comparative Outcomes Group
Bristol, United Kingdom

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Faculty
Arnold G. Vulto, PharmD, PhD, FCP
Professor of Hospital Pharmacy, Hospital Pharmacist and Pharmacologist,
Erasmus University Medical Center
Rotterdam, The Netherlands

Arnold G. Vulto, PharmD, PhD, FCP, has a financial interest/relationship or affiliation in the form of:
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Prof. Wojciech Jurczak, MD, PhD
Chair of Haematology, Jagiellonian University
Krakow, Poland

Prof. Wojciech Jurczak, MD, PhD, has a financial interest/relationship or affiliation in the form of:
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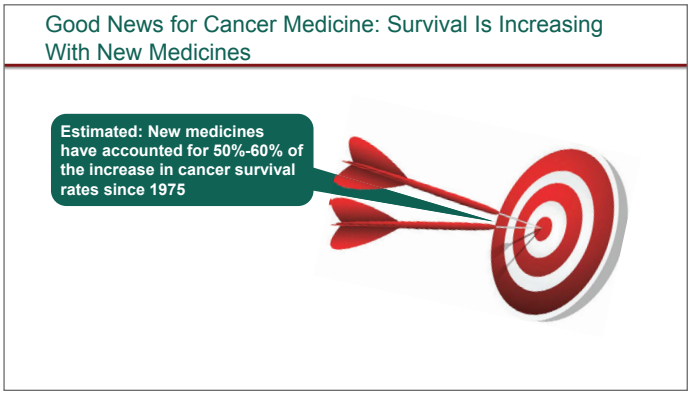
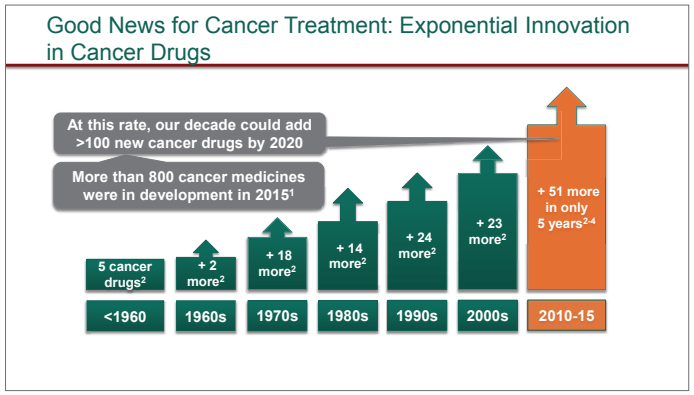
Paul Cornes, BA, BM BCH, MA, MRCP, FRCR
Comparative Outcomes Group
Bristol, United Kingdom

The Role of Biosimilars in Promoting Sustainability of Care

Now the first thing is to explain why so many of us are here—and that's because oncology is being transformed. Whilst it's important that our patients exercise, eat well, [and] give up smoking; let's hear it for what we actually do in terms of treatment. At least half the life-years saved over the last 30 or 40 years have come from what we do from our treatments and better treatments; and the tools that power us in medical oncology and haematology are anticancer medicines.





Reference(s): Lichtenberg FR. The Expanding Pharmaceutical Arsenal in the War on Cancer. National Bureau of Economic research Working Paper No. 10328. February 2004.

Paul Cornes, BA, BM BCH, MA, MRCP, FRCR: Good evening, colleagues, and thank you for coming for this hot topic on a hot evening. I know it's been a long day for many of you, but we're really pleased to have you here. We're going to talk about Biosimilars for Haematologic Malignancies and the Path to Sustainable Care. These are economic medicines [and] we need to make sure that they are as safe as they can be.

I'm Dr. Paul Cornes, an oncologist from Bristol in the United Kingdom with an interest in education, and I'm very lucky to have some expert colleagues with us today. Arnold Vulto is Professor of Pharmacology, but he's an important person here today, [given] his role with the Dutch Medicines Evaluation Board. We also have Wojciech Jurczak from Poland, who's been a key player and investigator in the pivotal trials that have led to the approval of both the rituximab biosimilars available in Europe.

Reference(s): 1. Medicines in Development for Cancer 2015 Report. PhRMA, September 11, 2015. http://www.phrma.org/report/medicines-in-development-for-cancer-2015-report. Accessed 20 June 2017.
Cornes P. Pictogram created from data in:
2. Savage P. *J Clin Oncol.* 2014;32(Suppl):Abstract e17535.
3. Lu D et al. *Cancer Chemother Pharmacol.* 2016;77:459-476.
4. US Food and Drug Administration (FDA). http://wayback.archive-it.org/7993/20170111064250/http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed 20 June 2017.

When our specialties started, we had very few [drugs]. But you'll see something remarkable has happened in the recent era, which is this dramatic turnaround between the lab discoveries—the bench-to-bedside time for transition. This is going to carry on, because at this rate we expect 100 new medicines to be in our pharmacy by 2020, and there are at least 800 separate molecules in the clinical trial stage as we speak. Now that's a wonderful time to be in this specialty, but it's difficult when you're the formulary pharmacists sourcing these medicines for your hospital, because many of these medicines are things we really want for our patients.

New Targeted Precision Medicines Are Transforming Cancer Care

In some cancers, survival has more than tripled

Cancer type	Old Model	Old Survival	Personalised Model	Personalised Survival
APL	Chemotherapy	19 mo	All-*trans* retinoic acid	>58 mo
CML	Chemotherapy	6 y	Imatinib	>22 y
Melanoma	Dacarbazine	<10 mo	Vemurafenib	16 mo
Medullary thyroid cancer	Chemotherapy	36 mo	Vandetanib	Not reached
GI stromal tumour	Chemotherapy	12-18 mo	Imatinib	Close to 5 y
Relapsed HL	Chemotherapy	1.2 y	Brentuximab vedotin	22.4 mo

Abbreviation(s): APL: acute promyelocytic leukaemia; CML: chronic myeloid leukaemia; GI: gastrointestinal; HL: Hodgkin's lymphoma.
Reference(s): Munoz J, Kurzrock, R. *Nat Rev Clin Oncol.* 2012;9:631-642; The Value of Medical Innovation. http://valueofinnovation.org/a-world-free-from-cancer/#ref3. Accessed 5 June 2017.

This is just some examples of diseases where survival has more than tripled by access to targeted therapy; and the only thing that seems to stand in our way from improving outcomes year on year is affordability.

We Have a Problem: Currently, Personalising Treatment Is Not Sustainable

CAN WE AFFORD THE WAR ON CANCER?

Immunotherapy vaccines could extend survival in a handful of cancers. But personalizing treatment, payers argue, is not sustainable. Where should the line be drawn?

BY ED SILVERMAN

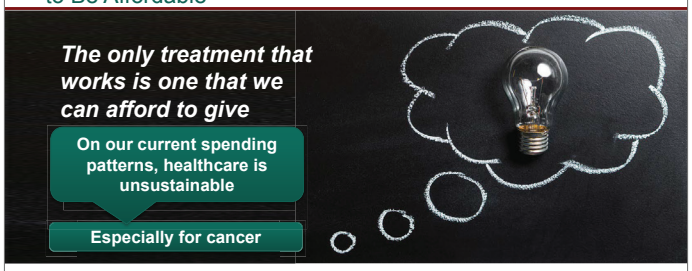
Two years ago, the U.S. Food and Drug Administration took a step that some thought would never occur—it approved the sipuleucel-T (Provenge) vaccine for late-stage prostate cancer. The move came after a protracted episode involving allegations of conflicts of interest among a pair of FDA advisory committee members who reviewed the ... tending a life by 4.1 months is worth the price of Provenge. It has also prompted larger questions about the underlying technology and the need to develop more vaccines.

Provenge is made by culturing a patient's immune cells with a recombinant antigen. The individualized product is then infused back into the patients, activating the immune system to target and attack the cancer. This "immunotherapy" underscores the move toward personalized

Reference(s): Brill S. "Bitter Pill: Why Medical Bills Are Killing Us". Time Magazine, 4 April 2013.
Silverman E. *Biotechnol Healthc.* 2012;9:13-16.

It will be a shame that this great process of personalised medicine fails for lack of investment, but you're aware we live in very hard economic times.

Access to Innovation Has One Key Rule: Treatment Needs to Be Affordable

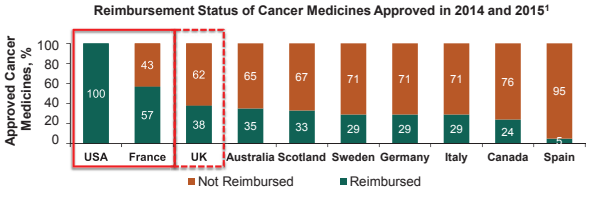


Reference(s): Cornes P. Personal communication, June 2017. Image: "Innovation", Creative Commons Zero (CC0), Public Domain. http://maxpixel.freegreatpicture.com/Inspiration-Innovation-Idea-Thought-Imagination-2123970. Accessed 17 May 2017.

And when I teach health economics, I tell them access to innovation only has one rule: The only treatment that works is one that we can afford to give. You can have the brightest idea, but if we can't translate it into clinical work, it won't help patients. And you need to know that on our current spending patterns, healthcare is unsustainable—and particularly so for us in cancer medicine.

Reimbursement of New Oncology Medicines Is Lagging in Many Countries

- Patients in only 2 countries had access to routine reimbursement for at least half of new oncology medicines launched in 2014-2015[1]
  - With the UK also reaching that access through a special "Cancer Drugs Fund"[2]



Reference(s): 1. IMS Institute for Healthcare Informatics Global Oncology Trend Report 2016. https://morningconsult.com/wp-content/uploads/2016/06/IMS-Institute-Global-Oncology-Report-05.31.16.pdf. Accessed 5 June 2017.
2. Aggarwal A et al. *Ann Oncol*. Epub 27 April 2017. doi: 10.1093/annonc/mdx110.

I'm not suggesting that, [in] every country, cancer's the most important disease; but how we handle this cost crisis and yet still afford to bring in innovation will be the model copied by other specialties. We know there is a crisis in reimbursement, even in the wealthiest countries. If you look at countries where patients had access to reimbursed drugs, at least half of the last 49 innovative medicines launched for oncology, you'll find

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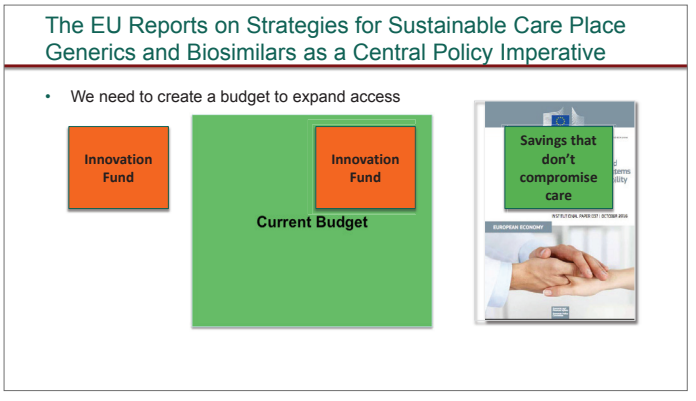
that only two nations routinely reimbursed those drugs, and a third one, the United Kingdom, joined that through special measures called the UK Cancer Drugs Fund. So we really have reached the limit for affordability.

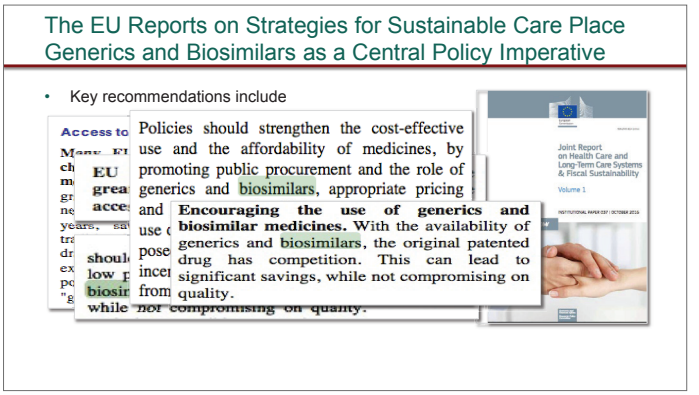
Reference(s): Thomas R et al. Delivering affordable cancer care a value challenge to health systems. Report of the World Innovation Summit for Health (WISH), Delivering Affordable Cancer Care Forum 2015. http://www.wish-qatar.org/summit/2015-summit/reports-en/delivering-affordable-cancer-care-en. Accessed 5 June 2017.

The reality of cancer care now from the WISH Report is very clear—you couldn't hear it any starker than this: Cancer care is not affordable for most patients, many payers, and nearly all governments. It's a real and immediate issue across the world.



Abbreviation(s): EU: European Union.
Reference(s): Cornes P. Personal communication, June 2017. Joint Report on Health Care and Long-Term Care Systems and Fiscal Sustainability, Volume 1, October 2016. EU. http://ec.europa.eu/economy_finance/publications/eeip/pdf/ip037_vol1_en.pdf. Accessed 5 June 2017.

So what do these biosimilars do? Well, the innovation we hear about today needs to be funded. It costs more than a billion dollars to develop a new cancer medicine, and very few of us have increasing budgets for cancer medicines to meet that innovation; so we have to fund that from somewhere. And whether it's the joint report from the European Union or the WHO 2010 report, More Health for the Money, it's clear we have to find it from savings within our current budgets, savings that won't compromise care for patients.

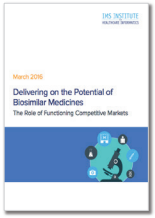


Reference(s): Joint Report on Health Care and Long-Term Care Systems and Fiscal Sustainability, Volume 1, October 2016. EU. http://ec.europa.eu/economy_finance/publications/eeip/pdf/ip037_vol1_en.pdf. Accessed 5 June 2017.

At the end of last year, the European governments produced this most important report about sustaining healthcare in Europe, and the key recommendation was to recognise the problem. It said over the next year, however, there would be opportunities to put this right and put healthcare on a sustainable level, and we should exploit these—it said—to the greatest possible extent by bringing in policies to support access to affordable medicines. And a theme comes though this document that you'll soon pick up: It's about generics and biosimilars, generics and biosimilars, generics and biosimilars.

The EU Notes the Potential Savings From Biosimilar Medicines

The cumulative potential savings to health systems in the five major EU markets and the US, as a result of the use of biosimilars, could exceed €50 billion in aggregate over the next five years and reach as much as €100 billion



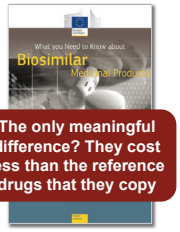
Reference(s): Delivering on the Potential of Biosimilar Medicines The Role of Functioning Competitive Markets. IMS Institute for Healthcare Informatics. March 2016. http://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Documents/IMS_Institute_Biosimilar_Brief_March_2016.pdf. Accessed 10 July 2017.

Now cheaper versions of drugs are no problem if they're of equal quality, and we can switch patients between versions of drugs. And we come under great pressure from our payers and our insurers, because they remind us that just five large countries, based on the expectations of savings and use, could save in the next five years somewhere between €50 and €100 billion.

I just want to remind you that it takes somewhere about a billion dollars to deliver a new cancer therapy, so we have at our grasp the funding for between 50 and 100 new cancer therapies if we can bring this safely to reality.

Does the EU Endorse Biosimilar Medicines?

- These are copies of patent-expired biologic medicines approved by a comparative "biosimilar" regulatory pathway
- They have the same indications, quality, safety, and efficacy of the original reference medicine
- They share the same International Nonproprietary Name ("INN")
- They have been in use in Europe for a decade with no evidence that they perform any differently than the original reference drugs



The only meaningful difference? They cost less than the reference drugs that they copy

Reference(s): European Commission Consensus Information Document: What you Need to Know About Biosimilar Medicinal Products. http://www.medicinesforeurope.com/wp-content/uploads/2016/03/biosimilars_report_en.pdf. Accessed 5 June 2017; EMA and the European Commission. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf. Accessed 5 June 2017.

What are biosimilar medicines that are so proposed by the European government? They are copies of patent-expired biologic medicines. They're approved by a comparative biosimilar pathway. They have the same indications, quality, safety, and efficacy of the original reference medicine. They share the same International Nonproprietary Name (INN), and we've used them in Europe for a decade with no evidence that they perform any differently from the original reference drugs.

We have more than 30 biosimilars approved over 10 years; we've used them for more than 400 million patients-days' exposure, and that's a remarkable record upon which we can teach the rest of the world.

The Promise of Biosimilar Medicines

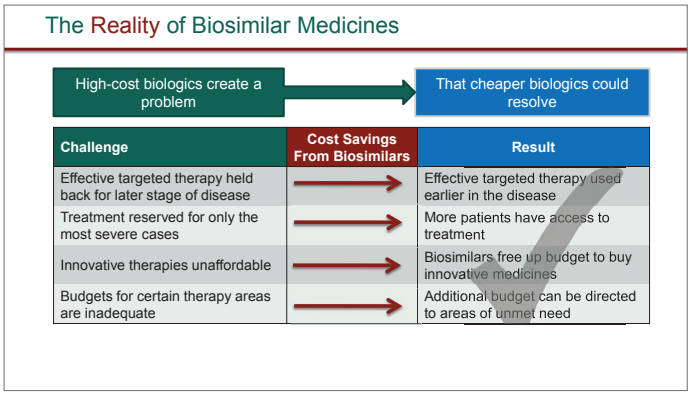
High-cost biologics create a problem → That cheaper biologics could resolve

Challenge	Cost Savings From Biosimilars	Result
Effective targeted therapy held back for later stage of disease	→	Effective targeted therapy used earlier in the disease
Treatment reserved for only the most severe cases	→	More patients have access to treatment
Innovative therapies unaffordable	→	Biosimilars free up budget to buy innovative medicines
Budgets for certain therapy areas are inadequate	→	Additional budget can be directed to areas of unmet need

Reference(s): Adapted from Henry D, Taylor C. *Semin Oncol.* 2014;41(Suppl 3):S13-S20.

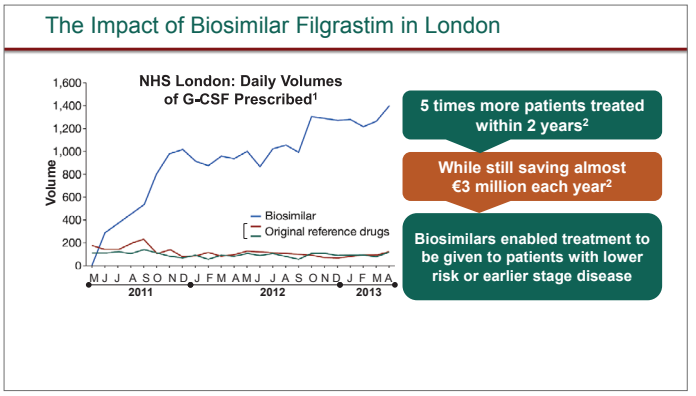
Now I told you at the start—these are economic tools, they're offering nothing that the original medicine didn't do before. But what they offer is a chance to increase access, because high-cost targeted therapies create a problem that cheaper, equally effective versions could resolve for us. At the moment, we hold effective therapy back for late stages of disease. We treat only the most severe cases, although the indications are often much wider. We can't afford innovative therapies because our budgets are too small.

Unless we think that drugs are the only things that save patients, remember, nurses save patients too. We shouldn't steal budgets that are critical for the holistic care of our patients. And so the economic test of these drugs is that they solve these problems; that we use these drugs in more patients at earlier stages of disease, releasing budget money to go back into the innovation budget or into other areas of need.



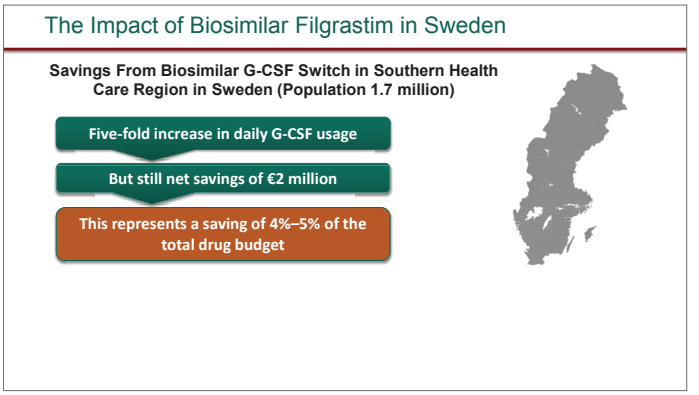
Reference(s): Adapted from Henry D, Taylor C. *Semin Oncol.* 2014;41(Suppl 3):S13-S20.

And, you know, after 10 years in Europe, we are very clear we have already proven that all of these steps are possible.



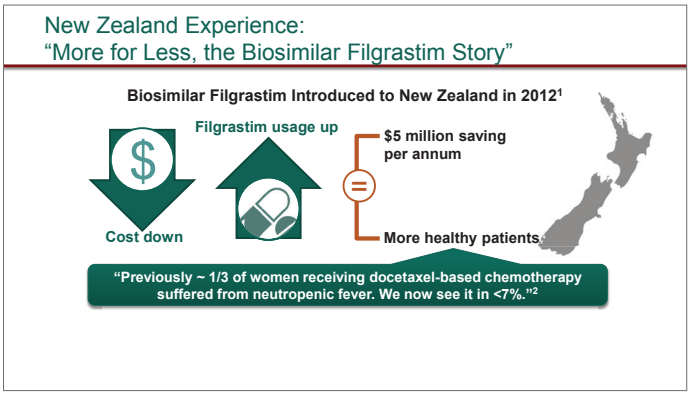
Abbreviation(s): G-CSF: Granulocyte-colony stimulating factor; NHS: National Health Service.
Reference(s): 1. Gascón P et al. Support Care Cancer. 2013;21:2925-2932.
2. Kashyap Thakrar. Biosimilar G-CSF: Implementation & lessons learnt. http://ccg.centreformedicinesoptimisation.co.uk/files/Kash%20Thakrar%20Biosimiar%20-%20GCSF.pdf. Accessed 10 June 2017.

And just in a few minutes I'll show you some evidence to back that up. This looks at the access to white-cell growth factor filgrastim to prevent neutropenia during chemotherapy in London; and the advent of biosimilars enabled more than five times more patients to access those treatments whilst still saving money to reimburse into the pan-London cancer drugs budget.



Reference(s): Gascón P et al. *Support Care Cancer.* 2013;21:2925-2932.

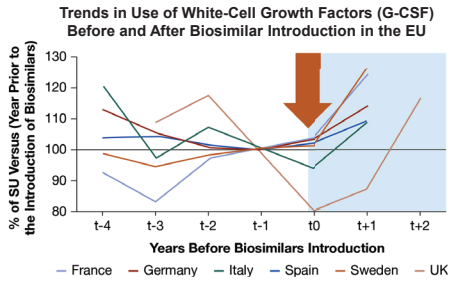
Biosimilars enable treatment to be given to patients with lower risk and earlier stage of disease, and it's nothing special to Britain because you can do the same in Southern Sweden; five times more access to these drugs, still returning savings back to the budget holders. And [with] just one drug, the use of a biosimilar could save between 4% and 5% of the total drug budget of your healthcare system.



Reference(s): 1. Biosimilar filgrastim: More for less – the biosimilar filgrastim story. PHARMAC Annual Review 2014. http://www.pharmac.health.nz/about/annual-review/2014/biosimilar-filgrastim/. Accessed 7 June 2017.
2. Filgrastim change - A view from the front line. PHARMAC Annual Review 2014. PHARMAC. http://www.pharmac.health.nz/about/annual-review/2014/biosimilar-filgrastim/filgrastim-sidebar/. Accessed 7 June 2017.

The benefit's seen to patients, as well. PHARMAC, our colleagues in New Zealand, told us that whilst they were able to save money from the advent of biosimilars, the principle benefit was for patients. They said: "Look, previously 1 in 3 women having chemotherapy for breast cancer would suffer neutropenic fever and require admission to hospital. Once biosimilars had expanded access, this risk fell to less than 7%".

Biosimilars Bring Treatments into Reimbursement That Might Otherwise Be Unaffordable



Reference(s): IMS Health. Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape. December 2011. http://weinberggroup.com/pdfs/Shaping_the_biosimiliars_opportunity_A_global_perspective_on_the_evolving_biosimiliars_landscape.pdf. Accessed 22 June 2017.

Wherever we look, the advent of approved biosimilars increases access for patients.

Biosimilars Reverse Negative Funding Decisions

- 2008 – NICE Technology Appraisal Guidance No. 142
  - Epoetin alfa, epoetin beta, and darbepoetin alfa are **clinically effective** for cancer treatment-induced anaemia
    - » **But not cost-effective**
- 2014 – NICE Technology Appraisal Guidance No. 323
  - Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy are **clinically effective**
    - » **And are now cost-effective at real contract prices**

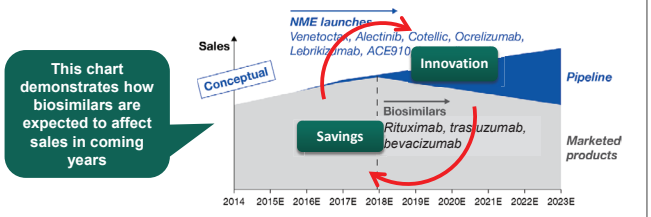
NICE accepted that biosimilar price competition had dramatically reduced the actual contract prices for epoetin

Abbreviation(s): NICE: National Institute for Health and Clinical Excellence.
Reference(s): NICE technology appraisal guidance [TA323] Published November 2014. http://www.nice.org.uk/guidance/ta323. Accessed 5 June 2017.
Image Road Sign CCO License; https://commons.wikimedia.org/wiki/File:Singapore_Road_Signs_-_Information_Sign_-_U-Turn_Lane.svg. Accessed 20 June 2017.

For countries like Britain and The Netherlands where decisions are often made using health technology assessments with cost-effectiveness criteria, we've shown that biosimilars can reverse a negative reimbursement decision. So, for example, in Britain the National Institute for Clinical Excellence looked at epoetins used to correct anaemia induced by chemotherapy during cancer treatment, and they decided these drugs were clinically effective but not cost-effective at their list price. But once biosimilar competition kicked in and there was a cycle of price reductions, they reversed that decision. They're clinically and cost-effective and can be used routinely in our health service.

Biosimilar Savings Fund Access to Innovative Therapy

- Innovative Pharma Manufacturers have outlined plans to adapt to biosimilars - using the savings to allow payers to reinvest in their next generation of innovation



Abbreviation(s): NME: new molecular entity.
Reference(s): Adapted from: Lorenzetti L. Biosimilars Are Coming After Big Pharma's Bottom Line. Fortune. http://fortune.com/2016/01/12/biosimilars-big-pharma/. Accessed 5 June 2017.

They also fund innovative therapy. We worry would biosimilars starve our innovative companies of their finance? But, look, some of the most innovative companies have briefed their shareholders and told them: "Look, although we may lose sales from patent-expired medicines, that will give the hospitals money to reinvest into our novel innovative agents".

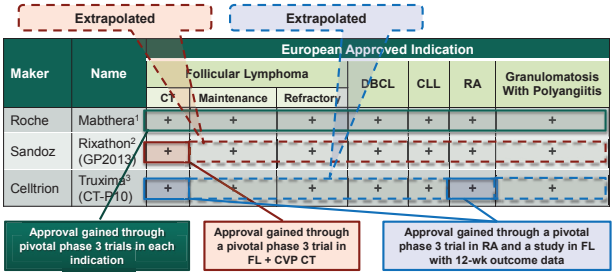
So by every measure of an economic success of these drugs, it's clear that they can achieve it.

Rituximab: Versions With European Approval[a]

Maker	Name	European Approved Indication (+)						
		Follicular Lymphoma			DBCL	CLL	RA	Granulomatosis With Polyangiitis
		CT	Maintenance	Refractory				
Roche	Mabthera[1]	+	+	+	+	+	+	+
Sandoz	Rixathon[2] (GP2013)	+	+	+	+	+	+	+
Celltrion	Truxima[3] (CT-P10)	+	+	+	+	+	+	+

[a] As of 23 June 2017.

Rituximab Extrapolation



Abbreviation(s): CLL: chronic lymphocytic leukaemia; CT: chemotherapy; DBCL: diffuse B-cell lymphoma; RA: rheumatoid arthritis.

Reference(s): 1. Rituximab (MabThera), SmPC. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf. Accessed 16 June 2017.
2. Rixathon, Summary of opinion. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/003903/WC500226219.pdf. Accessed 16 June 2017.
3. Truxima, Summary for the public. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004112/WC500222696.pdf. Accessed 16 June 2017.

Now we'd like to see the next generation of medicines achieve similar success, and as of this week you now have three versions of rituximab potentially that you could choose to use in your hospital; the reference drug rituximab, Mabthera, made by Roche, and two biosimilars, one from Sandoz that will be called Rixathon, but it was known in development as GP2013, and from Celltrion, Truxima, that in development was known as CT-P10.

Abbreviation(s): CVP: cyclophosphamide, vincristine, and prednisone; FL: follicular lymphoma.

Reference(s): 1. Rituximab (MabThera), SmPC. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf. Accessed 16 June 2017.
2. Rixathon, Summary of opinion. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/003903/WC500226219.pdf. Accessed 16 June 2017.
3. Truxima, Summary for the public. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004112/WC500222696.pdf. Accessed 16 June 2017.

Now it's going to be slightly more complicated than that. Remember, there are lots of indications that these drugs could be approved for, and the reference drug gained its approval through clinical trial proof—the so-called pivotal trial—whereas these drugs will often have gained their approval through extrapolation by focusing a pivotal trial on just one of the many indications, as long as we show the mechanism of action is the same; by proving that it's similar for one, we know it's similar for all. So, some of them [were] approved through follicular lymphoma trials, others mainly through pivotal trials in rheumatoid arthritis, buttressed by smaller trials in lymphoma.

And already the clinicians in the room can sense a challenge in explaining extrapolation to their patients, because the extrapolated indications grew out from the sameness of those trials.

Rituximab: Patent Laws and "Bio-Identicals"

Maker	Name
Roche	Mabthera
Sandoz	Rixathon (GP2013)
Celltrion	Truxima (CT-P10)

- Patents give the reference drug-maker a period of monopoly sales in exchange for disclosure about the product
- Patent-expiry permits other manufacturers to create biosimilar versions of the reference drug
- New patents can be granted with each new approved indication for a medicine
- **However,** since each country served by Europe's Medicines Regulator has a separate legal system, not all patents expire at the same time in every country

Rituximab "Bio-Identicals"

- Bio-identicals are the same drug but sold under different brand names

Maker	Name	Legally Approved Indication (+), Determined by Patent Dates						
		Follicular Lymphoma			DBCL	CLL	RA	Granulomatosis With Polyangiitis
		CT	Maintenance	Refractory				
Roche	Mabthera[1]	+	+	+	+	+	+	+
Sandoz	Rixathon[2]	+	+	+	+	+	+	+
	Riximyo[3]	+	+	+	+			+
Celltrion	Truxima[4]	+	+	+	+	+	+	+
	Blitzima[5]	+	+	+	+	+		+
	Ritemvia[6]	+	+	+	+			+
	Tuxella[7]	+		+	+	+		+

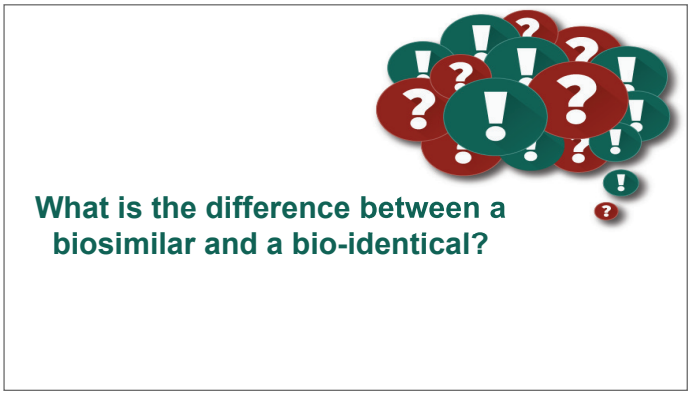
Reference(s): Brian J Malkin. Biosimilars patent litigation in the EU and the US: a comparative strategic overview. Generics and Biosimilars Initiative Journal (GaBI Journal). 2015;4:113-117.

There's another problem. Although Europe's regulator will span all of the European Union and other countries besides, remember that legal rules run in each country. And patents give the reference drug-maker a period of monopoly sales in exchange for their innovation. Patent-expiry permits other manufacturers to make a biosimilar copy, and the original drug-maker can increase indications at a later time again with new patent-expiry dates. And that means that whilst these drugs have been approved at a European level for every indication, this may not be so in your country.

Reference(s): 1. Rituximab (MabThera), SmPC. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf. Accessed 16 June 2017.
2. Rixathon, Summary of opinion. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/003903/WC500226219.pdf. Accessed 16 June 2017.
3. Riximyo-Summary of opinion. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004729/WC500226218.pdf. Accessed 3 July 2017.
4. Truxima, Summary for the public. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004112/WC500222696.pdf. Accessed 16 June 2017.
5. Blitzima-Summary of opinion. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004723/WC500228056.pdf. Accessed 3 July 2017.
6. Ritemvia-Summary of opinion. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004725/WC500228057.pdf. Accessed 3 July 2017.
7 Tuxella-Summary of opinion. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004724/WC500228059.pdf. Accessed June 23, 2017.

So I'm going to introduce a new term for you, drugs called "bio-identicals." These are the same drug but with different brand names that will be used in different territories due to patent expiry dates.

Now, fortunately, with all this complexity, I've got an expert in drug selection and someone who's run the trials in both these agents. So please don't forget to help me out by sending in all your questions.



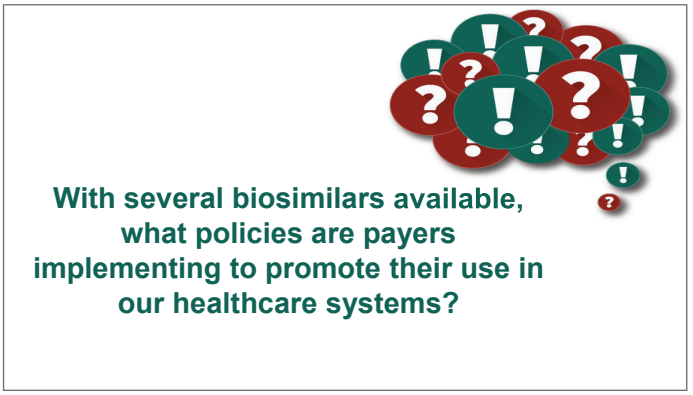
Dr. Cornes: So I'm just grateful for the questions that are coming in, and just perhaps to start you off, while I walk back over here, Arnold, I've got a question that's been texted in, and it says can you help us differentiate between a biosimilar and a bio-identical; I think for some of the audience we've sprung an entirely new term on them. Can you just give us the simple [answer] on this?

Arnold G. Vulto, PharmD, PhD, FCP: Yes, there's a simple answer on that. What we see in Europe now is that different countries have different rules for exclusivity rights for innovative drugs. So one system is just the patent, but there are additional exclusivity rules; for instance, if companies have also licensed a paediatric registration or they have a specific indication licensed there. So Europe is not just one continent, it's a patchwork now, and the companies have reacted to that by licensing the same molecule under two, three, or even four names. So the product from Sandoz has two brand names, and the Celltrion product has four brand names, and they tailor then the availability of the specific brand to the local situation regarding these exclusivity rights.

Dr. Cornes: So in terms of complexity, that means that for each country at present, you'll only have three options. Is that correct?

Prof. Vulto: Yes, that's correct. You won't have the seven options all available in your country because if the companies are wise, they will only market the drug that has an optimal set of indications that is possible for that particular country. So you have the innovative drug and at the moment then two biosimilars.

Prof. Wojciech Jurczak, MD, PhD: But from the doctor's perspective, it's very likely that we will have just one option, because working [in] the hospital, a doctor most likely will just prescribe rituximab and get what the pharmacy has.



Dr. Cornes: Arnold, you sit on a Medicines Evaluation Board, what are you doing to help bring the European governments' wish to use these drugs into action?

Prof. Vulto: Well, when it comes to payers, we discuss these things with the government insurance companies. In the Netherlands, we try to convince the insurance companies that they should not just take any savings right away, away from the hospital, because then there's no incentive for the hospital to move; that's one thing.

The second thing is that the tendering that we do, so the bidding for contracts.

Dr. Cornes: How do you manage that?

Prof. Vulto: We had a meeting on that with the European Commission a couple of months ago in May where we looked at the tendering how it's going on in Europe. And there's a European directive on tendering that is actually installed to improve freedom of trade in Europe; but the conclusion of that session was that [this] may not be the best outcome for healthcare systems, if we use tendering system. And especially if you have, say one tender with one winner—that usually does not improve competition. It's better to have [many] tenders so that you have more products there, they compete in the market.

I'm involved in a research consortium together with the University of Leuven, and there we looked at the generic market and we have seen that the generics market is optimal where you have at least three to four parties offering something, and it's better than just have one company taking it all.

How do you promote the best price discount for biosimilars?

Dr. Cornes: There's another question I've been asked. How do you promote the best price discount, and that's about reference pricing?

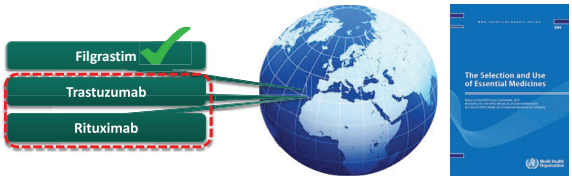
Prof. Vulto: Well, the reference pricing system is that one country is looking at the basket of other countries [and] what the price is in those countries—for instance, five or six countries—and they say, well, if in those six countries the price is level 80, then in our country we're not going to pay more than 80, that will be the maximum level of reimbursement. So that system is quite common now in Europe, but it's not very functional because it is based on list prices and not on actual negotiated prices, and the hospital market for medicines is quite often a negotiation market.

Dr. Cornes: So some of you may have seen just a few weeks ago a report produced by QuintilesIMS that looked at biosimilar competition in Europe and prices. And it could only, of course, use list prices, but it showed that it was the advent of competition that dropped the price, and I think interestingly, it dropped the price of the biosimilar, and, of course, the reference drug it was competing with. But it also did something we might not have expected— it dropped the price of other drugs in the same class. Is that a universal issue or is that just special to some classes of medicines?

Prof. Vulto: Well, we have seen it in the EPO market, we have seen it in the anti-tumour necrosis factor (TNF) market. You know, the anti-TNF market is quite young, actually, when [it comes to] biosimilars, but for the erythropoietin market, we know that it is happening.

Challenges to Haematology-Oncology Budgets Worldwide: WHO Essential Drugs List for Cancer, 19th Edition

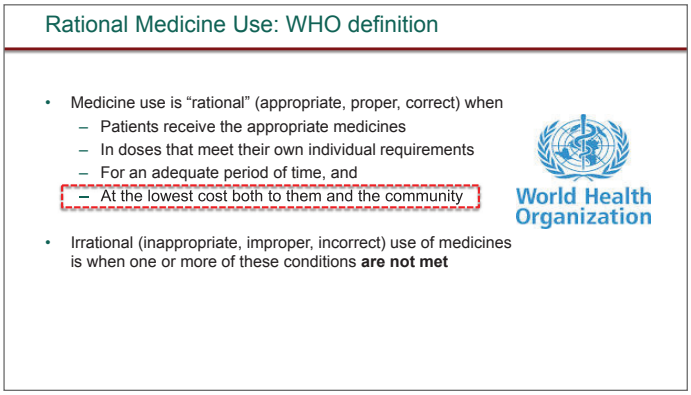
- Biologic drugs are now essential medicines for the world that we must provide free or at affordable prices to all appropriate patients
- Crucially, the latest WHO essential drugs list for cancer now includes 3 biologics



Abbreviation(s): WHO: World Health Organization.
Reference(s): 19th WHO Essential Medicines List, 2015. WHO. http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed 5 June 2017.

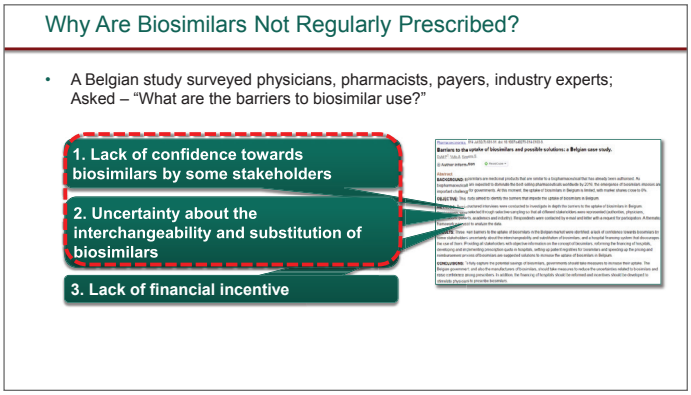
Dr. Cornes: Very good. Now, just to round up: One of the things that is most important for us is to think beyond the rich countries of Europe. Europe has 28 countries in the European Union, a few more besides within our regulatory zone, but the world is made up of 200 nations. And it's sobering to realise that three-quarters of all targeted therapy is used in just 7 of those 200 countries in the world, and that leaves 193 countries with the remaining 25%.

And biologic medicines that can transform outcomes are drugs that we need to provide for all healthcare systems, and the WHO signals the most important drugs through a list called the Essential Drugs List. The 19th update for the first time included some targeted therapies, traditionally high-cost medicines. One of them was filgrastim, and in a way we've had the biosimilar of this for 10 years and I've showed you the economic benefits. But the two others that they added that were biologics were trastuzumab and rituximab, and you've just seen the beginnings of this new class of therapeutic biosimilar oncology products.



Reference(s): WHO World Medicines Situation Report, 2011. http://www.who.int/medicines/areas/policy/world_medicines_situation/WMS_ch14_wRational.pdf. Accessed 22 June 2017.

Now to back up this demand that we really think cost effectively, many of you who know the old WHO prescribing rules will be surprised to see it's been modified. You're used to this. Medicine use is "rationale"—appropriate, proper, correct—when you use the right drug in the right dose and for the right schedule. But the three-step rules have been modified with a fourth – at the lowest cost to the patient and to society. And to hammer this home, the WHO really reminds us it's irrational, inappropriate, improper—incorrect to use medicines where any one of those conditions is not met. So it puts a heavy burden on us to justify why we don't engage with our payers in making this happen.



Reference(s): Dylst P, Vulto A, Simoens S. *Pharmacoeconomics.* 2014;32:681-691.

Now when you look at data across Europe, you'll find some drugs that have been available for 9 or 10 years; for example, biosimilar filgrastim where the use varies between 100% in some countries and 1% in another, and it's the 1% in Belgium that's often quoted. And so there's an interesting study that looked at what was driving that resistance, and the study suggested there were three key problems. The first was a lack of confidence by some of the stakeholders, whether they were physicians, pharmacists, or patient advocates. There was uncertainty about the role of switching, and the questions you're sending in there's a lot about that.

And the third was in the way of the lack of incentive. For a country that appears to have good access to rituximab, why in a way would you bother, it's nothing but trouble. Now I'm just sitting next to the author of this paper, so, Arnold, it seems that you've became a Belgian for the day. Can I get you up on the stand to perhaps take us through how you resolved those problems.

Prof. Vulto: So we did this study in the form of surveys. And what we are actually trying to do now in Belgium, and that's what's happening all over Europe, is that we are setting up educational programmes. The Minister of Health, actually she took action and she imposed a minimum use of biosimilars for the country, and that was a pact where both innovative industry and generic industry was involved.

And the lack of financial incentive had to do with the way hospitals were being financed. And it's curious to understand that, because as hospital pharmacists in Belgium, you were rewarded for the amount of discount that you could negotiate. Well, you can imagine if you buy an expensive product you can negotiate a higher discount than if you negotiate on a cheaper biosimilar. So there was a negative incentive to start using biosimilars.

Based on this paper, they have been changing the rules of reimbursement in hospitals and financing hospitals. So there's a lot of work being done, and we are continuing our research and following what is happening here.

Arnold G. Vulto, PharmD, PhD, FCP
Erasmus University Medical Center
Rotterdam, The Netherlands

A Look at Biosimilars Development

What Are We Talking About?

- ***The only true definition of a biosimilar as of June 2017:***
  - A biosimilar is a pharmaceutical product, that as such has been licensed via the EMA/FDA/WHO regulatory pathway (= minimum global standard)
- ***What does that mean?***
  - It is a version of an already licensed biotech-drug, for which similarity has been proven in an extensive ***comparability exercise***, encompassing physical, chemical, biological and pharmacological properties, including efficacy and safety
  - This excludes all kinds of *bio-questionables* in existence in other regions of the world that have not been endorsed via the WHO pathway as a biosimilar. *Reference to such products as biosimilars is incorrect*

GaBi
Generics and Biosimilars Initiative
Building trust in cost-effective treatments
www.gabionline.net

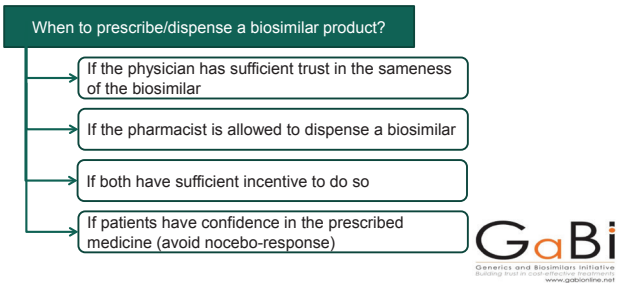
Abbreviation(s): EMA: European Medicines Agency; FDA: US Food and Drug administration; WHO: World Health Organization.
Reference(s): Vulto A. Personal communication, June 2017.

Arnold G. Vulto, PharmD, PhD, FCP: Although many of you will now be familiar with the general development paradigm of biosimilars, it's good to know that [a] biosimilar by itself, it's a legal invention—it's a product that has been licensed, so it's coined as a biosimilar by EMA or another advanced regulatory pathway, and those products went through the comparability exercise where they looked step-by-step at all the critical details of a molecule before starting using it in a clinical trial, and the clinical trial is a confirmatory trial.

So if doctors come to me to say" "Well, this is just a small trial and I don't understand the endpoints", then I say: "Well, it's not to prove efficacy—no, it's to prove it's doing the same [as the originator molecule]". But in addition to what I said before is that there are a lot of bio-questionables around in the world; so poor-quality drugs—Thailand, Indonesia, South America—and sometimes there are reports in the literature that they show, let's say, poor efficacy of immunogenicity or other side effects. And then people say: "You see, biosimilars are not good for us".

And I can tell you—and Paul said it actually, based on the report for the European Commission, [in] the past 10 years, there has not been a single major incident with any of the licensed biosimilars in Europe; so that should give trust.

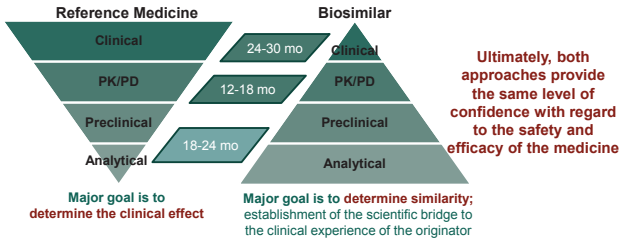
The Hot Potato: When Will a Physician Prescribe a Biosimilar and When Will a Pharmacist Dispense a Biosimilar Product?



Reference(s): Vulto A. Personal communication, June 2017.

So for me, then, if I talk about this in my hospital, then I know that there's a kind of a hot potato on the table: So when can we prescribe these drugs? First of all, the prescriber needs to have sufficient trust: Is this drug doing the same thing? The pharmacist should be allowed to dispense it; and they should [both] have incentive to do so. But also patients should have confidence in the prescribed medicine. And if they don't have this confidence, you can get a nocebo effect. Just by informing the patient that they will get another drug, and in this case maybe with [a] negative connotation, like, we are forced to use the cheaper alternative now, you are destroying part of the effect of the drug. The way you talk to your patients is very important [to] how they accept the drug.

Different Focus Between Originator and Biosimilar Development



Abbreviation(s): PD: pharmacodynamics; PK: pharmacokinetics.
Reference(s): Adapted from: Windisch J. *Int J of Clin Rheumatol*. 2015;10. http://www.openaccessjournals.com/articles/biosimilars-versus-originators-similarities-and-differences-from-development-to-approval.pdf. Accessed 7 June 2017; Martin K et al. http://www.santo.kz/en/doctors/publishing/european-experience-with-biosimilars/ Accessed 7 June 2017.

So this is the development model. On the left side: The reference medicine where the clinical work that you see on the top is really the heavy burden of the development; while on the right, you see that in the biosimilar [model], most of the work is being done in the laboratory. So we are making a perfect copy of the molecule, and then we confirm in a clinical trial that the product is good and safe to use.

For a Decision to Prescribe a Drug, Information Is Needed

- Biosimilars are not *identical* but *similar*
  - What does that mean?
  - What are then the differences and what could be the consequence?
- A deep understanding of bio-equivalence and "biosimilarity" is not easy
- Uncertainty will be smaller if we know the safety profile—both for originator medicines and biosimilars
- Biosimilars are standing on 10-15 years of experience of innovator medicines

Physicians don't like uncertainty
When in doubt, do not cross!

GaBi
Generics and Biosimilars Initiative
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Reference(s): Vulto A. Personal communication, June 2017.

But then we come to the message to you, well these drugs are not really identical. And then you have the right question: Well if they are not identical what are the differences and what are the consequences for my patients? So you need to understand principles like bioequivalence or biosimilarity, and it's not easy. And because of that uncertainty, we see a lot of reluctance in many countries in Europe by doctors to use these drugs; because while they have been familiar with the originator for about 10 years, now there's this drug with uncertainty.

Biosimilars Licensed by EMA Since 2006[a]

Molecule	Approval	Brand Name
Somatotropin	2006	Omnitrope
Epoetin alfa	2007	Abseamed; Binocrit; Epoetin Alfa Hexal
Epoetin zeta	2007	Retacrit; Silapo
Filgrastim	2008	Biograstim; Ratiograstim; Tevagrastim
Filgrastim	2009	Filgrastim Hexal; Zarzio
Filgrastim	2010	Nivestim
Infliximab	2013	Inflectra; Remsima
Follitropin alfa	2013	Ovaleap
Filgrastim	2013	Grastofil
Follitropin alfa	2014	Bemfola

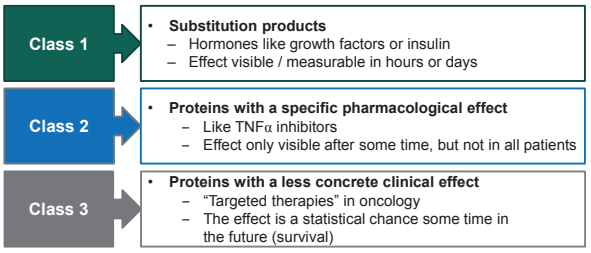
Molecule	Approval	Brand Name
Filgrastim	2014	Accofil
Insulin glargine	2014	Abasaglar
Etanercept	2016	Benepali
Infliximab	2016	Flixabi
Enoxaparin-Na	2016	Inhixa; Thorinane
Insulin glargine	2016	Lusduna
Teriparatide	2016	Movymia; Terrosa
Rituximab	2016	Truxima
Adalimumab	2017	AmgevitaSolymbic
Etanercept	2017	Erelzi
Rituximab	2017	Riximyo; Rixathon
Rituximab	2017	Blitzima; Tuxella; Ritemvia
Insulin Lispro	?	Insulin Lispro Sanofi

[a] As of May 2017; not available in all countries.

Abbreviation(s): EMA: European Medicines Agency.
Reference(s): EMA website. http://www.ema.europa.eu/ema/. Accessed 7 June 2017.

This is what is available at the moment in Europe. So there are about 30 biosimilars now licensed; this looks like a long list, but you have to segregate them in three classes.

Three Classes of Therapeutic Proteins (Biopharmaceuticals)



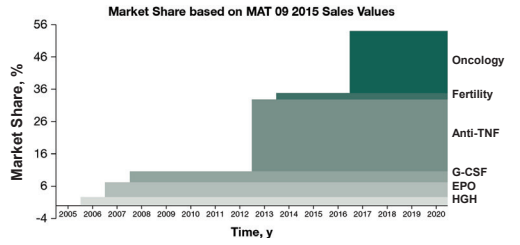
Abbreviation(s): TNF: tumour necrosis factor.
Reference(s): Schellekens H et al. *Lancet Oncol*. 2016;17:e502-e509.

The first class is the first class that we had in the market—these are substitution products. And in my hospital, at least, most people are not bothered anymore [by] which kind of G-CSF (granulocyte-colony stimulating factor) or epoetin we are using; 10 years ago that was a different story. What is critical here [is] if you inject the drug you see an effect in a relatively small time in almost 100% of your patients.

The class 2 is somewhat different. These are proteins with specific pharmacological effect, like the TNF- inhibitors. There you see an effect only after some time—6 weeks, 3 months or so in rheumatoid arthritis; and not in all patients; like in inflammatory bowel disease (IBD), these drugs are effective in about 60% of the patients. So the observability of the clinical efficacy of the drug is very difficult and you have to accept the research data.

And I think it's important to understand these things, because in oncology and haematology [class 3], it's even more difficult because there, the effect actually is a statistical chance sometime in the future—5-year survival, 10-year survival, etc.; so it's even more difficult, the observability of the drug effect.

Size of Therapy Classes Exposed to Biosimilar Competition (in Sales) Versus Total European Biologics Market



Abbreviation(s): HGH: human growth hormone.
Reference(s): IMS Health. The Impact of Biosimilar Competition June 2016. http://www.egaevents.org/presentations/2016bios/Per_Troein.pdf. Accessed 7 June 2017.

And you see the importance of this class on the market, on the bottom line; you see the first-class G-CSF, EPO and human growth hormone (HGH), then the anti-TNFs. And now just in 2017, as you can see on the right side of this figure, we are on the top with the oncology drugs like, rituximab and trastuzumab.

Third Class: Therapeutic Proteins With a Remote Clinical Effect

- These protein drugs provide a statistical chance on benefit some time in the future (eg, trastuzumab, rituximab)

- We need deep trust in the principles of similarity
  - On what is the purported (usually rather weak) clinical effect based?
  - Can we expand the use in other types of cancer?

Reference(s): Vulto A. Personal communication, June 2017.

So there's a lot to be gained there by finding cheaper alternatives. So, as I said, they provide a statistical chance and you need to understand the principles of biosimilarity; and then an additional thing that you need to understand is that these drugs are being investigated in a particular indication and patient population, which is going to be sensitive not to show efficacy, but to show a difference. So we are not going for, let's say, the largest clinical effect; no, we go for such an effect that we are able to detect differences if they are there.

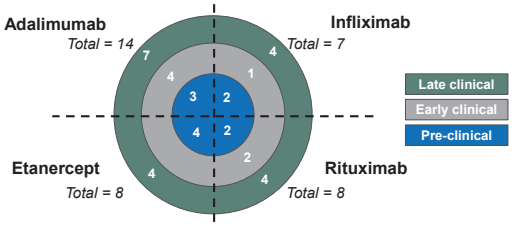
Biosimilars in Registration

- 11 Biosimilars in registration (EMA) as of 15 May 2017
  - Adalimumab (2x, Boehringer Ingelheim, Samsung)
  - Bevacizumab (2x)
  - Insulin glargine (1x)
  - Pegfilgrastim (2x)
  - Trastuzumab (4x; Celltrion, Mylan, Samsung, Amgen)

Reference(s): EMA, Applications for new human medicines under evaluation by the Committee for Medicinal Products for Human Use, May 2017: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/05/WC500227100.pdf. Accessed 7 June 2017.

There are still 11 biosimilars in the pipeline, and it's expected that in 2020, we may have about 70 biosimilars. So it's imperative that you have a good understanding of the value of these drugs.

Estimate of Biosimilars in Development for Four Key Biologics



Reference(s): Adapted From: IMS Health. Delivering on the Potential of Biosimilar Medicines: The Role of Functioning Competitive Markets. March 2016. http://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Documents/Institute%20Biosimilar%20Media%20Webinar%20March%2024%202016.pdf. Accessed 7 June 2017.

Here you see the pipeline for four molecules; for adalimumab there are 14 molecules in development. And we may end up with 20/25 different brand names because of all the exclusivity problems. For etanercept, there will be 8; infliximab there'll be 7; and rituximab there are 8. This is a graph from March 2016, so at the outer dark green circle there are 4 rituximabs, and 2 have now reached the market and 2 are soon to follow.

Top 25 Pharmaceutical Companies and Investment in Biosimilars

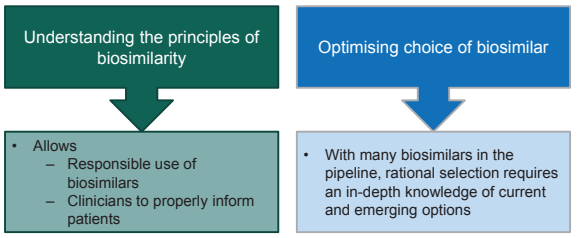
Rank	Company	Investment in Biosimilars: Yes / No
1	Pfizer	**Yes**
2	Novartis	**Yes**
3	Roche	No
4	Merck US	**Yes**
5	Sanofi	**Yes**
6	Gilead	No
7	J & J	No
8	GSK	No
9	AstraZeneca	**Yes**
10	AbbVie	No
11	Amgen	**Yes**
12	Allergan	**Yes**
13	Teva	**Yes**

Rank	Company	Investment in Biosimilars: Yes / No
14	Novo Nordisk	No
15	Eli Lilly	**Yes**
16	Bayer	No
17	BMS	No
18	Takeda	No
19	Boehringer Ingelheim	**Yes**
20	Astellas	No
21	Mylan	**Yes**
22	Biogen	**Yes**
23	Celgene	No
24	Merck KGaA	**Yes**
25	Daichi Sankyo	**Yes**

Reference(s): Moorkens E et al. *Front Pharmacol.* 2017:8:314. doi: 10.3389/fphar.2017.00314.

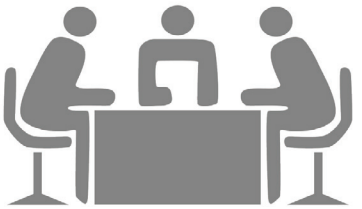
And is this a success story in the pharmaceutical industry? Well, we did a study and we looked how at the moment, the top 25 of most money-intensive companies are investing in biotechnology and biosimilars. And the majority of those companies now are investing in that; and there's the minority like Roche or GlaxoSmithKline (GSK) or AbbVie who have decided, no, at this moment we are not going to do it yet. But most companies now are involved in that, which means that the old paradigm, 'well, you have these generic companies and they make these cheap drugs' is no longer true; that our first-line companies like Pfizer, Novartis, Merck, Sanofi are now in developing biosimilars. So they produce [with] the same standards as they produce the innovative drugs.

Summary



So in summary, it's critical for you as prescribers to understand the principles of biosimilarity; that it's necessary for responsible use of the biosimilars, and only then you are able to inform your patients. And in the end, if there's a lot to choose, you should be able to differentiate between different products. Because we have so many products in the pipeline, a rational choice of those products is essential. But there you can always call the pharmacy and ask them to help you. I thank you very much for your attention.

Questions



Should physicians trust the process of similarity comparison in the context of regulatory guideline recommendations? If so why?

We expect to have several rituximab biosimilars available shortly, will you use them?

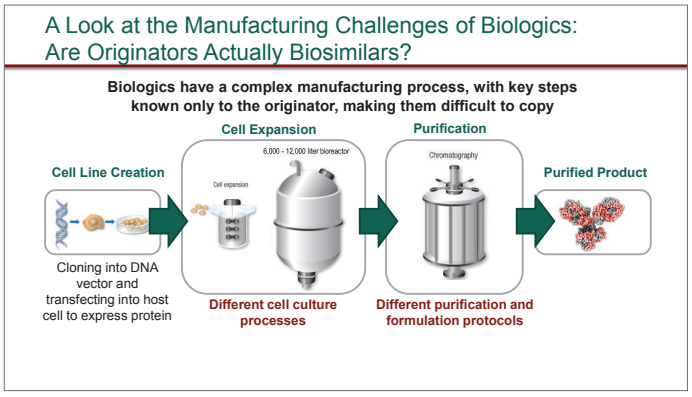
Paul Cornes, BA, BM BCH, MA, MRCP, FRCR: Now I think, Arnold, you gave us a hint there, you said "rational choices—to ask the pharmacist." So the question that I've been sent in is basically should we trust the process of similarity in the context of the guidelines, and if so why? We expect to have several rituximab biosimilars—that's two more potentially to launch in each country. Will you use them, and how would you explain that confidence to your physician colleagues at the Drug and Therapeutics Committee? So, just on rituximab.

Prof. Vulto: Yes, I can answer that for rituximab. When rituximab actually was introduced on the market and you started using it, it was a black box drug—you didn't know how it worked. Is it true or not; you saw a clinical effect and you trusted that. Nowadays we know where in the molecule the signals are, there are four to five major signals, we know exactly where on the molecule, we can look into the molecule and we test this in the laboratory. We call that "critical quality attributes".

If I look at the development process of a biosimilar for rituximab, there are about 60 to 70 critical quality attributes that are relevant in assessing: "is the biosimilar molecule doing the same"; "Is it the same and doing the same than the reference product"? And this is done with technology that was not available, let's say, 20 years ago. In the early days of biosimilars, people were saying, well, it's impossible to characterise a molecule. Today I can say it's possible to

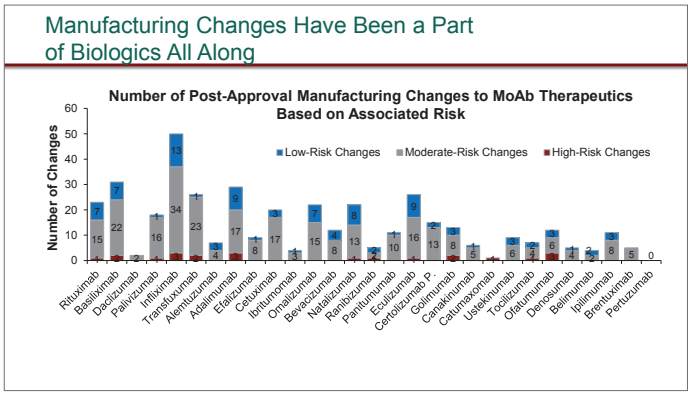
characterise a biological molecule almost to perfection; we have all this modern technology like mass spectrometry and all the other technologies that we have. So I have high trust in all these technologies.

Prof. Wojciech Jurczak, MD, PhD: And this preclinical development is absolutely necessary to develop biosimilar, but if you're still not convinced, we had over 1,200 patients treated in Sandoz clinical trials, over 700 patients treated in Celltrion clinical trials, so those were enough patients to register the originator particle.



Reference(s): Adapted from: Al-Sabbagh A et al. *Semin Arthritis Rheum*. 2016;45(5 Suppl):S11-8.

Prof. Vulto: Also, here you have to understand a little bit how biologics are being manufactured. If you see on the left-hand side, it starts by cloning the DNA of a certain protein into a cell; it [then] has to be expanded, you have to grow it in large barrier reactors, although the size of that is downsized also. There's a lot of purification going on; and all these steps are critical in getting a pure and safe compound in the end.



Abbreviation(s): MoAb: monoclonal antibody.
Reference(s): Vezér et al. *Curr Med Res Opin.* 2016;32:829-834.

But these processes are being optimised all the time, and that's public information. If you go to the website of European Medicine Agency, then you can trace back, for all these products, what kind of manufacturing changes there have been. And this was actually summarised in a paper by Vezér in 2016 where for most of the monoclonal antibodies—so etanercept is not there—they looked at all these manufacturing changes. And if you see the highest bar is there for infliximab—there are about 50 [changes]. And then you see three colours.

So the light blue is low-risk changes, that's a change in label, etc. It doesn't matter really. The moderate-risk change is, for instance, the change in the filter system that may affect the quality of the outcome. And on the bottom you see the [red-] brown blocks. These are really very small, these are high-risk changes where, for instance, they changed the cell system. And you see then that all these products, they have undergone moderate-risk and high-risk changes.

This is being closely monitored by the European Medicine Agency. Every time again after such a change, the company has to go to the EMA and they are evaluating this. And based on that experience actually, they developed the biosimilar pathway. It's a similar technology that they used. And so the consequences of that are, for instance, you see that changing a filter supplier—so not the filter system, the filter supplier—is a low-risk. But a new cell line on the right-hand side, you can imagine that is a major risk.

And it's interesting to see that even innovator companies, they sometimes are being sent back to the drawing table when they come up with a new molecule and the EMA says, well, we don't buy that, it's not good enough, you have not been able to reproduce your own molecule. And with the same scrutiny, they look at biosimilars. And I think this is a vast experience there and I trust that.

Dr. Cornes: Now, Arnold, obviously people were listening up when you told us that analytics had moved on so forward so you could characterise everything. So the question says if your bioanalytical methods are so sensitive, do you need a clinical trial at all?

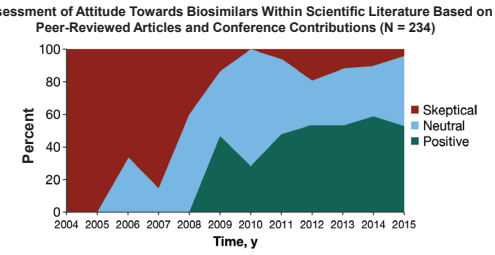
Prof. Vulto: That's a very good question, and that question has been answered now by the EMA. It may be difficult for you to accept, but yes it's possible to license a biosimilar without clinical trial. Actually, there are now biosimilars being licensed without clinical trial. So, molecules that have been characterised so accurately by physical/chemical techniques and by a bioequivalence trial—so it's not a clinical trial in terms of efficacy and safety but in terms of pharmacokinetics—and if the bioequivalence is determined, the EMA now accepts this as proof of biosimilarity.

Given the manufacturing changes that occur over time with originator molecules, could the biosimilar drugs stop being biosimilar to the originator in the future?

Dr. Cornes: Now I've been given a question about the manufacturing change points you brought up which said if these drugs are biosimilar now, will they be biosimilars 5, 10, 15 years in the future?

Prof. Vulto: That's a question that was unanswered by EMA for about five, six years, and they now have two answers. The first is they keep the originator product in the same margins as the biosimilar. So they require that if the originator product is developing/evolving, those certain critical quality attributes should stay within the same margins as they have been originally. The second remark is it's impossible for a biosimilar company to follow an originator drug that's going to be changed. So, EMA has decided now that once a biosimilar drug is being licensed and there's a change going on in the originator then the biosimilar medicine will be looked upon as an independent licensed registration. So it will not harm the biosimilar.

Summary



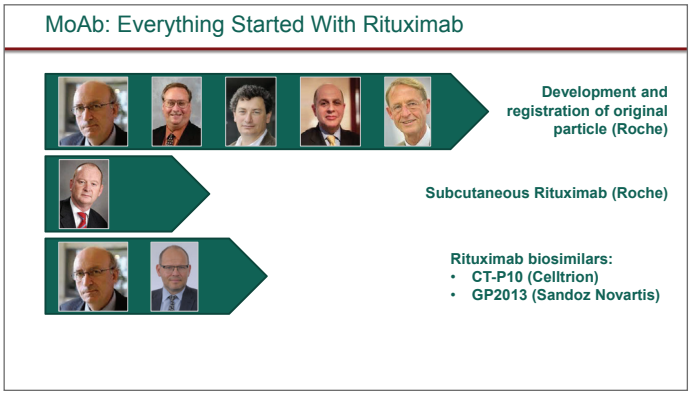
Reference(s): Image adapted from Daubenfeld T et al. *J Business Chemistry.* 2016;13(1). http://www.businesschemistry.org/article/?article=218. Accessed 7 June 2017.

Dr. Cornes: I think from what Arnold told us, about a decade ago there was a real disbelief that this would actually work. But this is a very important paper that looks at the theme in peer-reviewed papers about biosimilars over time. And you'll see that our initial scepticism about this class of drugs in a way has been passed.

So, our conclusion here, [is] we've had a decade of use of these drugs, more than 400 million patient days. They don't seem to have—in any of our studies—any clinical difference in safety and efficacy. We know from the data so far that the ones we've had can be switched under the supervision of a physician. We have clear evidence already they're succeeding in their economic role by expanding access to patients and recycling money back into the innovative drug fund.

Prof. Wojciech Jurczak, MD, PhD
Jagiellonian University
Krakow, Poland

The Role of New Molecule Innovation in the Sustainability of Treatment for Haematologic Malignancies

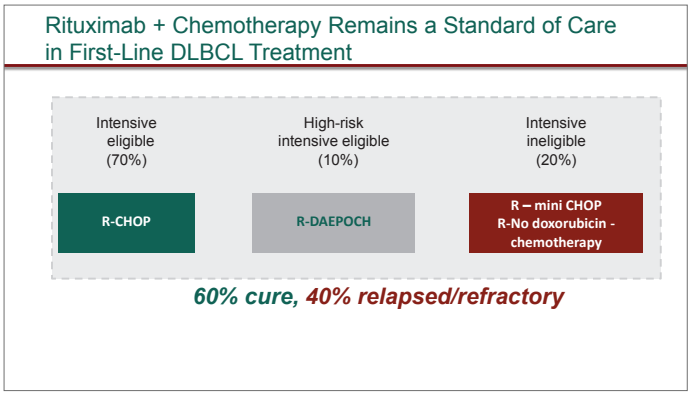


Abbreviation(s): MoAb: monoclonal antibody.

Prof. Wojciech Jurczak, MD, PhD: Paul, thank you very much for inviting me here. After the excellent presentation you and Arnold had in pharmacoeconomics and legal issues, my task is simple.

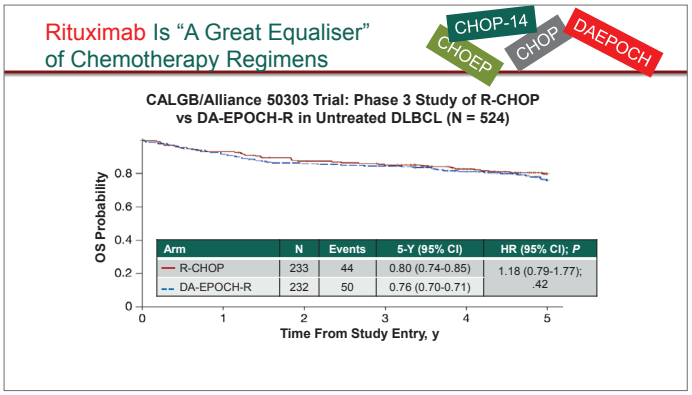
Now, we got accustomed to the use of biosimilars; we don't use original epoetin (EPO) or original granulocyte-colony stimulating factor (G-CSF); we just use biosimilars in everyday medical practice. And so what happened with rituximab? We just built on the arm of giants. So, all big names, who created the original particle, then a subcutaneous (SubQ) rituximab, and now we have biosimilars.

So, my target here will be just to remind you that everything started from rituximab, at least the targeted therapy in non-Hodgkin lymphoma started [with] rituximab. And so we use it in first-line in all of the cases, sometimes first-line in maintenance [as well].



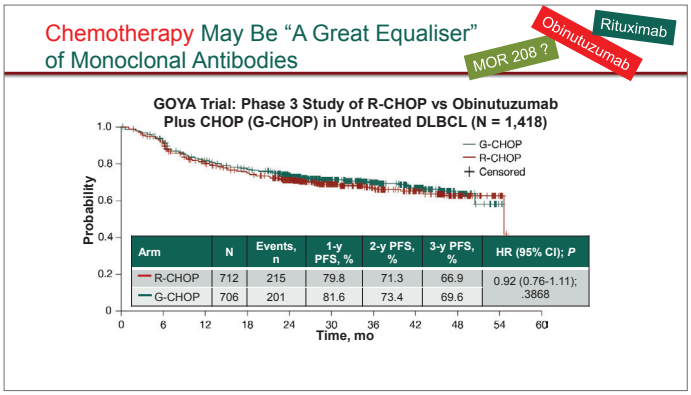
Abbreviation(s): DLBCL: diffuse large B-cell lymphoma; R-CHOP: rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone; R-DAEPOCH: rituximab + dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone.
Reference(s): Based on: NCCN guidelines. https://www.nccn.org/about/nhl.pdf. Accessed 22 June 2017.

So starting with diffuse large B-cell [lymphoma], we do agree that with all the modern chemotherapies and all the other monoclonal antibodies, R-CHOP is still like Britannia—it rules the waves.



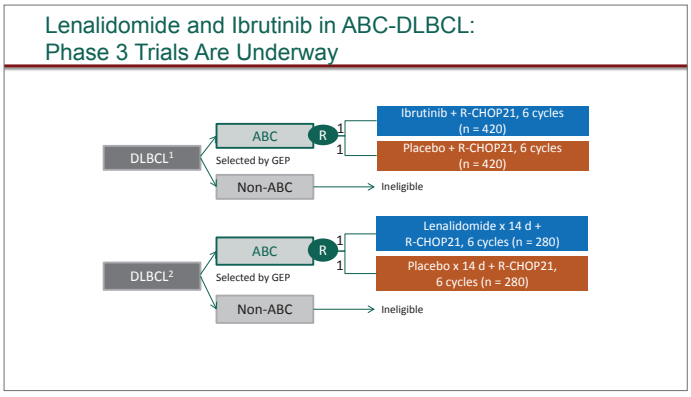
Abbreviation(s): CHOEP: cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone; OS: overall survival.
Reference(s): Wilson WH et al. *Blood*. 2016 128:469.

And, let me just convince you that rituximab—we called it a great equaliser, because regardless of [the chemotherapy] we used—CHOP-14, CHOEP, or whatever—the results were similar. And so it happened with dose-adjusted EPOCH: In the randomised setting, we could find no difference.



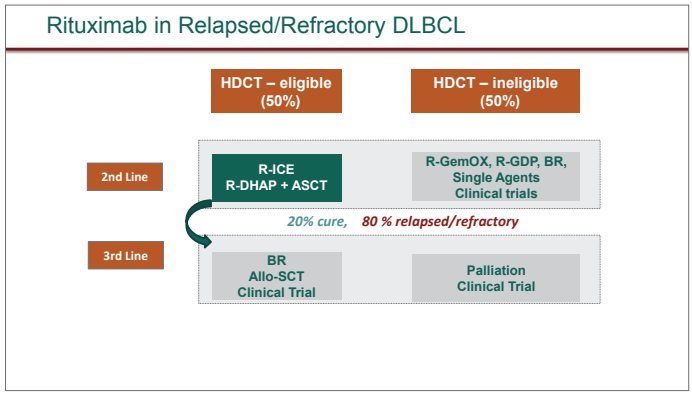
Abbreviation(s): PFS: progression-free survival.
Reference(s): Vitolo U et al. *Blood.* 2016.128:470.

However, let me just draw your attention to another fact. We had 1,400 patients randomised in this trial, and it looks like CHOP is a great equaliser—at least intensive chemotherapy—might be the great equaliser for the even better monoclonal antibodies—because we do have better monoclonals like obinutuzumab. But maybe combining its effect with CHOP is not adequate. Therefore, rituximab is still the standard of care in diffuse large B cell [lymphomas].



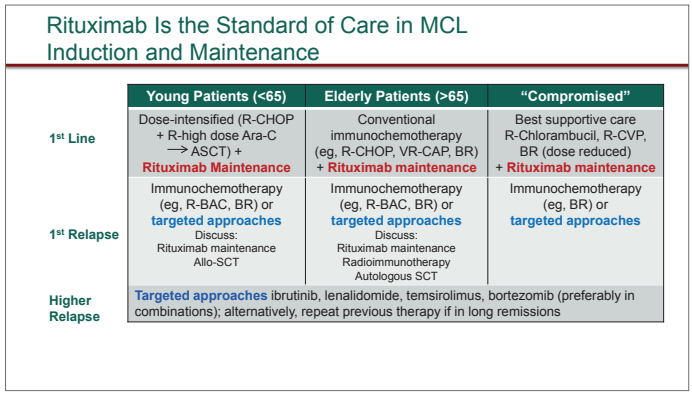
Abbreviation(s): ABC: activated B-cell like.
Reference(s): 1. ClinicalTrials.gov Identifier: NCT01855750. 2. ClinicalTrials.gov Identifier: NCT02285062.

Well, I mean, we tried to improve [upon] it; we have all the data concerning the small particles—the B-cell receptor pathway and the others. So, we have the trial with ibrutinib, which is completed. We're just completing the ROBUST trial with lenalidomide. But again, it's adding something and not replacing rituximab.



Abbreviation(s): ASCT: autologous stem-cell transplantation; BR: bendamustine-rituximab; Gem: gemcitabine; HDCT: high-dose chemotherapy; Ox: oxaliplatin; R-GDP: rituximab-gemcitabine-cisplatin-dexamethasone; R-ICE: rituximab-ifosfamide-carboplatin-etoposide.
Reference(s): Based on: NCCN guidelines. https://www.nccn.org/about/nhl.pdf. Accessed 22 June 2017; Dreyling M et al. ESMO, MCL guidelines. 2017. In press.

[If we're] talking about the relapsed/refractory setting, well, we need to transplant everyone who is transplantable—yes, we know it; but the role of transplant is decreasing because the better the first-line therapy, the worse the transplant results. All that is left is clinical trials, most of them with rituximab.

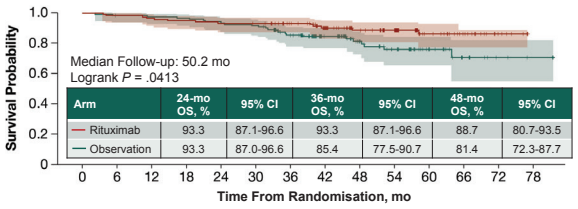


Abbreviation(s): Ara-C: cytarabine; MCL: Mantle-cell lymphoma; R-BAC; rituximab, bendamustine, cytarabine; VR-CAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone.
Reference(s): Dreyling M et al. ESMO, MCL guidelines. 2017. In press.

Switching to what's not registered—but it doesn't mean that we don't have solid data—namely to mantle-cell lymphoma. These are the recommendations that Prof. Dreyling will publish in ESMO, in the next couple of months.

MCL: Rituximab Maintenance in "Younger Patients"

LyMa Trial: Phase 3 Study of Rituximab Maintenance Versus Observation After ASCT in Young Previously Untreated Patients With MCL (N = 240)



Arm	24-mo OS, %	95% CI	36-mo OS, %	95% CI	48-mo OS, %	95% CI
Rituximab	93.3	87.1-96.6	93.3	87.1-96.6	88.7	80.7-93.5
Observation	93.3	87.0-96.6	85.4	77.5-90.7	81.4	72.3-87.7

Reference(s): Le Gouill S et al. 58th Annual Meeting of the American Society of Hematology (ASH 2016). Abstract 145.

So, what's new is rituximab maintenance for everyone. We used to have maintenance for the elderly, but now we have a trial by Le Gouill, which [was] presented at the last ASH [meeting], that showed we need to have rituximab maintenance for the transplanted patients as well. In fact, we're not trying to find out whether to use a maintenance [therapy] or not, but what should we use in maintenance—so whether rituximab alone or rituximab with ibrutinib or something else.

For the younger patients, the question is the same. We use immunochemotherapy upfront plus maintenance with rituximab or maybe plus lenalidomide or plus ibrutinib. Therefore, we have all the marvelous drugs, but they are used for the second line.

Need to Consider "Long Road Ahead" in Management of Indolent Lymphomas to Allow Multiple Lines of Therapy

Slow, careful management will allow patients to receive further treatment later on

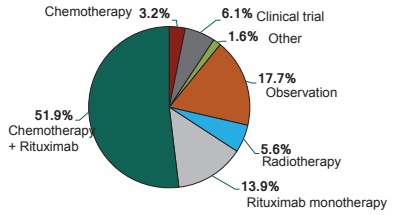
During their lifetime, patients with iNHL may get 4-7 immunochemotherapy lines of treatment

Abbreviation(s): iNHL: indolent non-Hodgkin lymphoma.

Indolent lymphomas are not curable. If we can't cure it, we have to treat it as leisurely as possible. Why? With the pace, with the speed of improvement we have nowadays, we can't say that we will not be able to do the job in five or 10 years. But, we have to treat the patients in a way that we will be able to treat them later. So I tend to tell my patients that it may well happen so that although the average lifespan in indolent lymphomas, at the moment, is 15 years, maybe for them [it] will be 20 or 30. Maybe follicular lymphoma will be just like diabetes or hypertension—the disease we have, we live with but we don't die from. So, having this road in mind, we need to have something to treat the patients with later on because we do not have an indefinite number of ploughs.

Chemotherapy Without MoAb Is Not Regarded as a Standard of Care in iNHL

US Clinical Practice, SEER Data: Initial Therapeutic Strategy in Patients With Follicular Lymphoma (N = 2,728), 2004-2007

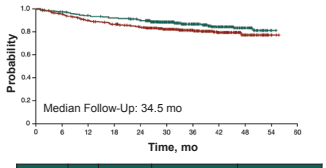


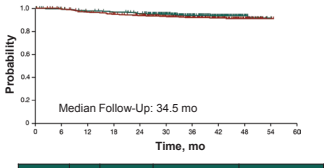
Abbreviation(s): SEER: Surveillance, Epidemiology, and End Results (database).
Reference(s): Friedberg JW et al. *J Clin Oncol.* 2009;27:1202-1208.

So, what do we start with? Definitely not just chemotherapy; nobody uses chemotherapy, not even the Americans. So do we need the very, very high-tech chemotherapy upfront? Do we need the very best monoclonals upfront? In my opinion, no; because if we want to keep the patient alive for the next 10, 15, 20 years, we want to have something to treat them in the relapsed and refractory disease setting.

Follicular Lymphoma: Rituximab-CT vs Obinutuzumab-CT Followed by Maintenance in First-Line Treatment

GALLIUM Phase 3 Trial: Rituximab-Based Versus Obinutuzumab-Based Induction and Maintenance (N = 1,202), Primary Results





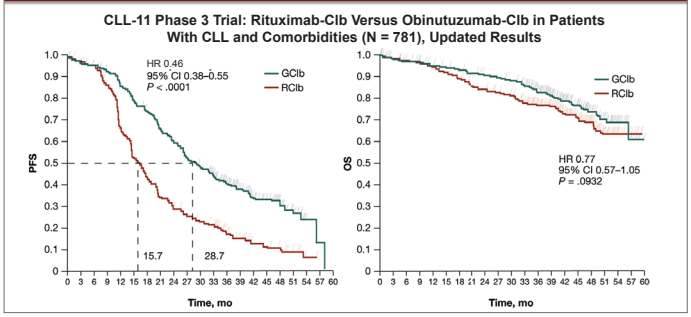
Arm	n	Events, n	3-Y TTNT, % (95% CI)	Stratified HR (95% CI); P
G-CT	601	80	87.1 (84.0-89.6)	0.68 (0.51-0.91); .0094
R-CT	601	111	81.2 (77.6-84.2)	

Arm	n	Events, n	3-Y OS, % (95% CI)	Stratified HR (95% CI); P
G-CT	601	35	94.0 (91.6-95.7)	0.75 (0.49-1.17); .21
R-CT	601	46	92.1 (89.5-94.1)	

Abbreviation(s): CT: chemotherapy; TTNT: time to next treatment.
Reference(s): Marcus RE et al. 58th American Society of Hematology Annual Meeting (ASH 2016). Abstract 6.

So again, these are the trials that were done—magnificent trials – but as you see, no overall survival difference whatsoever. So again, despite [the fact that] we have a better monoclonals, rituximab is still pretty good.

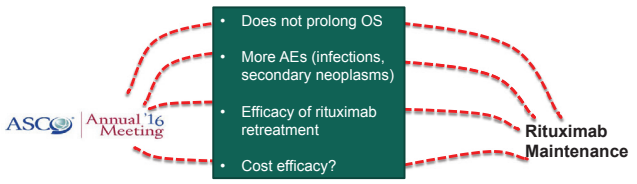
CLL: Rituximab-Clb Versus Obinutuzumab-Clb in Previously Untreated Patients With Comorbidities



Abbreviation(s): Clb: chlorambucil.
Reference(s): Goede V et al. 57th Annual Meeting of the American Society of Hematology (ASH 2015). Abstract 1733.

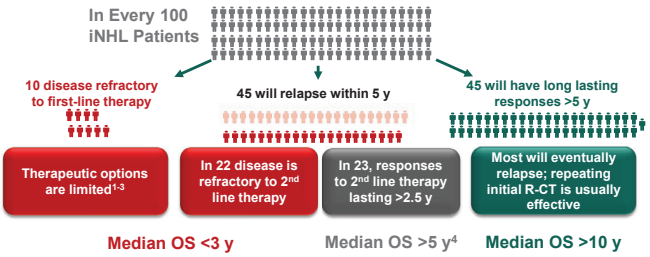
Conversely, in CLL, we have a difference, because in this case we use the better monoclonal antibodies. We have chlorambucil, which is just a very weak chemotherapy; so in a subset of populations, in the elderly not tolerating chemotherapy [for example], rituximab might not be the treatment of choice.

Is Maintenance Rituximab Still the Standard of Care in iNHL?



Now, talking about rituximab maintenance, we still use it, although it suffered some heavy shelling at ASCO last year, namely because it didn't prolong overall survival; it provoked some adverse events; [and] there were questions about cost efficacy. But again, the less important/the less intensive the chemotherapy, the more the maintenance does.

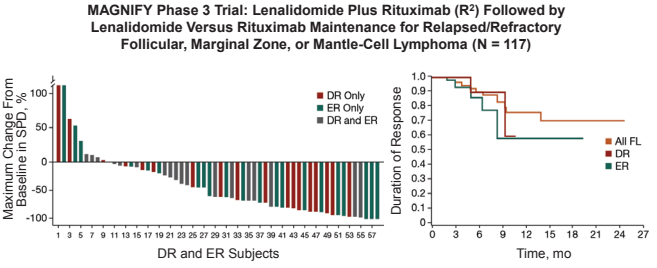
Selecting iNHL Patients with Unmet Medical Need



Reference(s): 1. Kahl B et al. *Cancer.* 2010;116:106-114.
2. Horning SJ et al. *J Clin Oncol.* 2005;23:712-719.
3. Czuczman MS et al. *Blood.* 2012;119:3698-3704.
4. Van Oers MH et al. *J Clin Oncol*. 2010;28:2853-2858.

So, I think we can quite safely stick to the old rituximab in the setting of a good responding patient or those who relapse late. Now there is an unmet medical need in those who do not respond to therapy or those who relapse early.

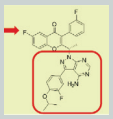
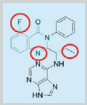
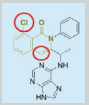
Relapsed/Refractory iNHL: Lenalidomide + Rituximab



Abbreviation(s): DR: double refractory; ER: early relapse
Reference(s): Andorsky DJ et al. ASCO 2017. Abstract 7502.

If I were to point out a single breakthrough in lymphoma, it was this trial presented at ASCO. But, am I wrong? It's again rituximab with lenalidomide. So a non-chemotherapy option for relapsing/refractory setting. So despite all the marvelous particles we have, rituximab is holding strong.

iNHL: Make PI3K-Delta Great Again

TGR-1202	Idelalisib (GS-1101)	Duvelisib (IPI-145)
		
Delta	Delta	Delta/Gamma
QD	BID	BID

Reference(s): Burris HA et al. *J Clin Oncol*. 2015;33 (suppl): Abstract 7069; O'Connor O et al. 57th Annual Meeting of the American Society of Hematology (ASH 2015). Abstract 4154; ClinicalTrials.gov Identifier: NCT02793583; Idelalisib, product monograph. http://www.gilead.com/~/media/Files/pdfs/medicines/oncology/zydelig/zydelig_pi.pdf. Accessed 5 June 2017.

Ah, not talking about politics, we have alternatives.

Rituximab as a Standard of Care in First-Line B-Cell Lymphoma Treatment

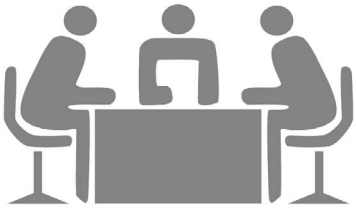
Lymphoma Subtype	First-Line Induction	First-Line Maintenance
Aggressive lymphomas	√	X
MCL	√	√
Indolent lymphomas	√	√
CLL	√	√

The only alternative to IV rituximab biosimilars in first-line B-cell NHL therapy is… subcutaneous rituximab

Reference(s): Rituximab (MabThera), SmPC. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf. Accessed 16 June 2017.

This is my summary slide: So everything started from rituximab. We use it in the first-line in all of the cases; sometimes in maintenance. So I think that the only alternative to intravenous rituximab—or rather to say to rituximab biosimilar—is the subQ rituximab. Thank you.

Questions

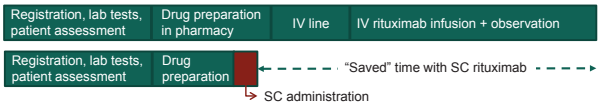


Should we switch from a biosimilar to a bio-better if it is available?

Dr. Cornes: Now I've got a question sent in, and this is about bio-betters. So the question asks when there are bio-betters available—for example, subcutaneous versions of these drugs—what's the role of a biosimilar?

Prof. Jurczak: We have to be rather cautious about defining bio-betters, because if we look at rituximab, for example, we are receiving now a bio-better from the rituximab that was manufactured and sold 20 years ago. Because most of those drugs, they undergo post-registrational changes which we doctors are not even aware of—[and are] possibly changed for better.

Subcutaneous Rituximab: A New Quality of the Old Drug



Now talking about subcutaneous (subQ) rituximab is something different, because if you're able to deliver the same monoclonal in a shorter infusion of just subQ jab—10 minutes—then it may result in a shorter hospital stay. The patients might be less tired, and get fewer infections at the end. So it's very difficult because there are no trials that address this, and that has to be decided on a personal basis.

If a patient is started with IV rituximab, can they be switched to subcutaneous rituximab for the maintenance or consolidation phase?

Dr. Cornes: Now I've got a question here that says if we started treatment with a rituximab biosimilar through the intravenous route, would it then be okay to switch to subcutaneous for a monotherapy maintenance or consolidation phase?

Prof. Jurczak: That's the only way—we can't give subQ rituximab as a first exposure. We may use subQ rituximab only in the patients who did not develop any reactions to the first intravenous infusion.
However, the most common clinical situations we'll face is that we have to have the first dose of IV rituximab, and whether we [then] want to go for subQ rituximab [or not]. Then the patient develops a reaction, and for the patients who are actually developing some kind of immune reactions, therefore cannot get a subQ rituximab later, should we switch or should we not to a biosimilar? I don't think we have an open answer to that yet.

Are there data to suggest that some biosimilars may be different in terms of immunogenicity and infusion-related reactions?

Dr. Cornes: Now, you've seen the data in these papers coming out. Just a followup, there's been a question: Are there any data on infusion-related reactions or other side effects to suggest that they're different? So, this is about immunogenicity and presumably you've collected all that data. What's the feeling so far?

Prof. Jurczak: Nothing very much different. All we've learned is statistical error limits. They are very good quality products, all of them.

Prof. Vulto: What we see now is that with most biosimilars, infusion reactions are more or less the same. Antibody formation is more or less the same. We have seen one exception, and that is with etanercept, where it looks as if the injection of the biosimilar is less painful for the patient. Actually it's a very nice example here that when Amgen was developing the biosimilar for adalimumab, it was very clear in the trials that it was less painful, and that made AbbVie to hurry up to come up with a subcutaneous form that was less painful too. Unfortunately, they changed the concentration. So now we have an innovative product in a high concentration and the biosimilar in a low concentration. But that's the competition that we see happening in the market. But we monitor all these aspects.

Paul Cornes, BA, BM BCH, MA, MRCP, FRCR

Arnold G. Vulto, PharmD, PhD, FCP

Prof. Wojciech Jurczak, MD, PhD

Ask the Faculty

Dr. Cornes: Now, we've just got a little bit of time left and I've got a barrage [of questions] for you here that I can put up on the screen.

Will there be new indications for biosimilars and other trials initiated even after approval?

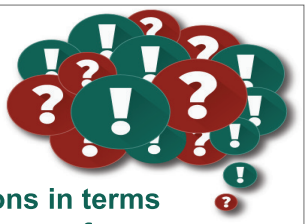
Dr. Cornes: So, this is a good one, which is do the trials stop once the drug is approved, or are there further trials running on these drugs for other indications or for more security?

Prof. Vulto: Well, for more security, it's very important that we see that happening now; actually, it's also happening with the rituximab, but we see it happening with the tumour necrosis factor (TNF)- inhibitors, that the licensing trials are just short-term trials, so for one year. But now for TNF- inhibitors we have already a three-year trial experience with those drugs because they are used chronically. And in haematology it's slightly different because not all your patients live for three years.

Dr. Cornes: Are the trials that you were involved with, are they going to continue with further data collection, going to get longer outcomes?

Prof. Jurczak: Absolutely. I mean, the trials are still ongoing. There are trials in rheumatology investigating the possibility of switching between biosimilars and originators. There will be trials where we will investigate the question of the length of infusion. So, yes, we will still carry on.

Prof. Vulto: Another very important aspect in the licensing of all biological medicines in Europe, including biosimilars, and that is postmarketing surveillance. So if a product is being licensed, there is residual uncertainty—that's the legal term that's being used by the regulators. This residual uncertainty—so open questions—is being translated in a risk management plan. And that's part of the package that the company has to fulfil. And in most conditions, companies have to follow up with patients—2,000, 3,000 patients—to document that treatment-documented exposure, we have all the results. So it's not just stopping with the trials, there's a lot of follow-up work.



What are the considerations in terms of potential off-label use of biosimilars?

Dr. Cornes: We know in inflammatory disease that off-label use of this drug is quite common. So, Arnold, when you're trying to keep control of medicines in your hospitals, how do you differentiate between off-label use that's good and off-label use that's bad?

Prof. Vulto: Well, we have quite an extensive ruling on that in our country, which works very well. There are two important aspects to that. First of all, if a doctor is going to use a drug outside of its indication, they can discuss that with the pharmacist. And if they both together decide well this is best care, standard practice, etc., it's not a problem. And the same thing is that our medical societies sometimes have included non-licensed indications in the guidelines as being best practice, and that's also accepted in the Netherlands as good practice at that time. So, in the Netherlands, we are going with that quite easily. I know in the US it's different – it's more strict and legalised. But, if things are either in the medical guidelines from the specialist organisations or it has followed the rule well, we have been discussing this with the pharmacist so it's a peer decision, then the doctor is at least protected against legal action.

How should physicians and pharmacists prescribe/dispense and monitor biosimilars?

Dr. Cornes: We know that prescribing sometimes falls below standard. So, Arnold, what are the rules, what do you want to see doctors doing in prescribing these drugs so you can track and trace them?
Prof. Vulto: For biological drugs, there's the European guideline telling us that if you prescribe a biological drug, that you have to monitor the brand name and the batch number. Well, can I see hands who is doing that? I don't see many hands, so we are all sinners, then in relation to that particular guideline.

Dr. Cornes: Isn't the truth that the doctors rely on the pharmacist, you and your colleagues, to do this for us?

Prof. Vulto: Well, we won't do it either; so the pharmacists are not doing it either. We are able to track down the brand of the drug, but in most countries we are not able to track down the particular batch of the drug.

Dr. Cornes: So let's be clear, the new directives on smuggled and counterfeit medicines are bringing in an absolute requirement that all hospitals in Europe will have to comply with. So in terms of prescribing in Europe, we will write the international nonproprietary name plus the brand, and then somewhere there's another step for that vigilance programme.

Prof. Vulto: The system that the industry is implementing is just a system where they look at where the drug is coming from and where it's being dispensed, and although the information is available, it will not be automatically monitored.

So now we are discussing with our Minister of Health that by implementing this anti-counterfeit directive, that she should also implement the registration of the batch number.

If pharmacists are not currently registering the specifics of the products delivered to patients, should physicians be concerned then in terms of safety and immunogenicity, given that the patient is likely switching between several biosimilar versions of rituximab?

Dr. Cornes: Right. Now, I've got a colleague standing up here. Can you introduce yourself and ask your question?

Audience Member: There are several tenders in the country, that means also that several of these biosimilars are on the market; and especially in lymphoma patients [who] will move from city hospitals to university hospitals when they may need a transplant—So they are probably faced with the use of two or maybe three biosimilar versions of the rituximab.
And the European Medicines Agency (EMA) has the rule that pharmacists should register which product is delivered because of the immunogenicity. And if you are now saying that you are not registering which product is delivered to the patient, [does] that mean that you are not considering the immunogenicity problem as serious?

Dr. Cornes: Thank you. It's a very important question. So this is really about the safety of switching brands. So we know from our experience with the first-generation biosimilars—that's the first class of the growth factors, filgrastim and epoetin over 10 years— that switching on a tender basis is certainly safe. We know from the second-class biosimilars, ones that perhaps we're not used to—the anti-inflammatory biologics like TNF inhibitors—that, again, there are now substantial data on the safety of switching. But, Arnold, how do you answer that question when it comes up at your drug and therapeutics panels?

Prof. Vulto: It is a point of concern especially for highly immunogenic drugs, and rituximab is now one of them. So we need to track down what particular biological the patients are being treated with. And if the patient, for instance, comes back to the university hospital or goes the other way around, we should, in essence, [until] we have further evidence—because it may, as Paul was saying, it may resolve this problem, yes, we should keep the patient on the same drug.

And we see that confirmed now with the TNF- inhibitors, where they've shown that for the infliximabs that there's 100% identical immunogenicity between the two compounds that are available now; that's proven.

Dr. Cornes: And in Europe over 10 years, we've never seen any evidence that a biosimilar has a different immunogenicity, and there are already very good independent academic studies of the most challenging drugs, so think about the murine antibodies, the mouse-derived ones in diseases where anti-drug antibodies are very common. So anti-antibodies are the signature mechanism of disease in rheumatoid arthritis, and this may explain, of course, why a biosimilar reference, a biosimilar pivotal trial in rheumatoid disease could be useful.

Dr. Cornes: Wojciech, when it comes to a next Drug and Therapeutics board before the next tenders, how will you decide? Is it just going to be on price? Are there any other criteria that you use to select the drug of choice given the three you're likely to have to choose from this year?

You're going to have an originator and two biosimilars. How would you make that decision?

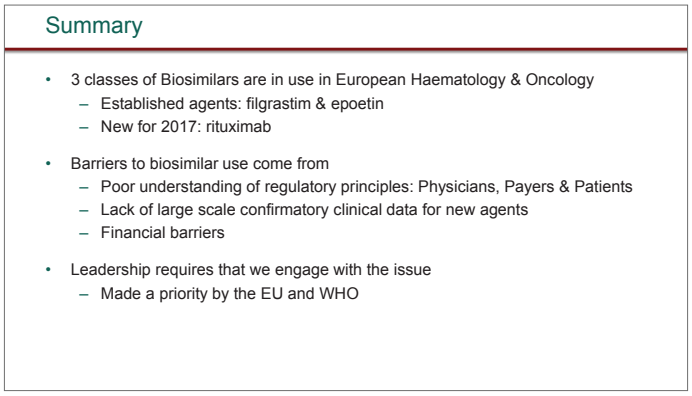
Prof. Jurczak: I'm fortunate that we don't have to make this decision because someone else will. But personally, I think that there is no difference. We have the trials, we have the special biosimilar registration pathway. And we, as the doctors, we should be able to decide whether you want to treat the patient with a subcutaneous (subQ) drug or intravenous drug. And there are regulations for it. But apart from this, it doesn't matter.

Prof. Vulto: Well, I see differences. As a pharmacist, I see differences in the way the drug is being made available in different strengths, for instance, which from my perspective, as a pharmacist in a hospital with both adults and in children, it's critical. I see difference in stability. I see differences in usability and standard conditions for other biosimilars. I see differences in administration devices. So I always tell people don't go for the lowest price, go for the best product that is the best feasible for your working situation. And that may not be the cheapest.

Dr. Cornes: So best might be delivery times, might be injection devices, things like these seem to be [important for the decision]?

Prof. Vulto: Well, to give just a very simple example, for instance, in our hospital, we have a centralised reconstitution unit, as is happening in more and more hospitals in Europe. It means that stability of your product is essential. Some of the innovative products they have really poor documentation; they have the information that's not in the package insert. They say it's eight hours, for instance. Well, if we are running a clinic on the Tuesday after Easter, we want to produce those infusions on a Friday. And the company that has provided stability data that we can produce them on a Friday and use it on a Tuesday—that has a preference; that has a bonus point in the selection process. Just give you a simple example.

Prof. Jurczak: That's why teamwork is always better.



Dr. Cornes: Now look in the last couple of minutes, do you think there's any topic that we should cover just before I wind up that you want to talk about?

Prof. Vulto: Well, I find it important that, as doctors, you should speak up in your hospital. That you should unite together with your pharmacist and maybe your hospital management [team] that you are involved in selecting the drug that you think is most appropriate for your clinical practice. I think it's important.

Prof. Jurczak: I absolutely agree with your one voice, specifically in front of the patients. Because we know what the difference in biosimilars are. But if we exaggerate with that and if we just exaggerate in underlining those differences, the patients are totally lost. And what we do know for certain—out of the whole biosimilar registration pathway and the result of clinical trials—that there is no difference from the patient point of view. We can treat them as efficiently and as safely with all the three drugs registered.

Dr. Cornes: Well thank you, colleagues. So, in summary, three classes of biosimilars are in use in European haematology and oncology. We've established 10 years of research and practical use of white cell and red cell growth factors. But new for us this year is rituximab biosimilars, and we have a steep learning curve. We've understood that barriers to biosimilar use come from poor understanding of the regulatory pathway by all of us—physicians, payers, and patients. We've heard from Wojciech that it's about making friends with your specialist pharmacists that may be the way out of that.

It's of the nature of these drugs that large-scale confirmatory clinical trials aren't there as they are for new agents, but Wojciech pointed out that by the time you add all the trials together we are talking about what, more than 2,000 patients for the two drugs so far. Some of the barriers to use may not be ones that we, as doctors, create; they may be financial problems. Leadership requires that we do engage with this issue whether it's as a society, as the European Societies of Haematology and our medical oncology groups, whether we do it at a national level or just at our hospital level, we do have to show leadership. Remember what the WHO told you about rational and irrational prescribing. So thank you very much for having been here.

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