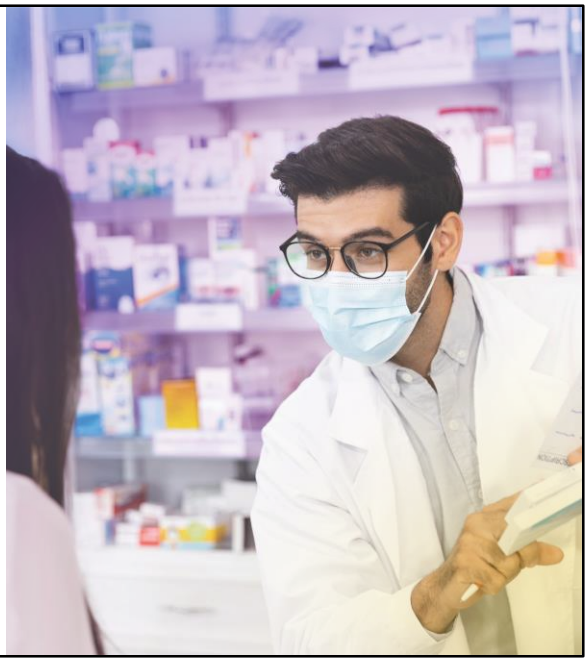
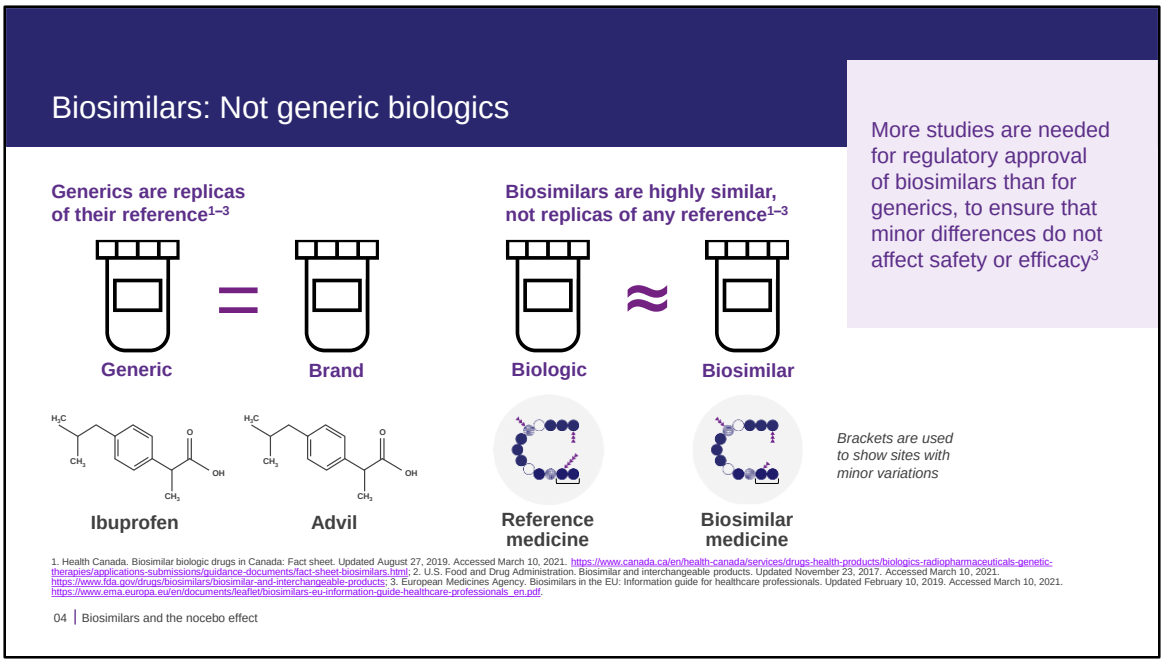

Biosimilars and the nocebo effect:
A practical guide to helping patients transition to biosimilars

Summary

Biosimilars

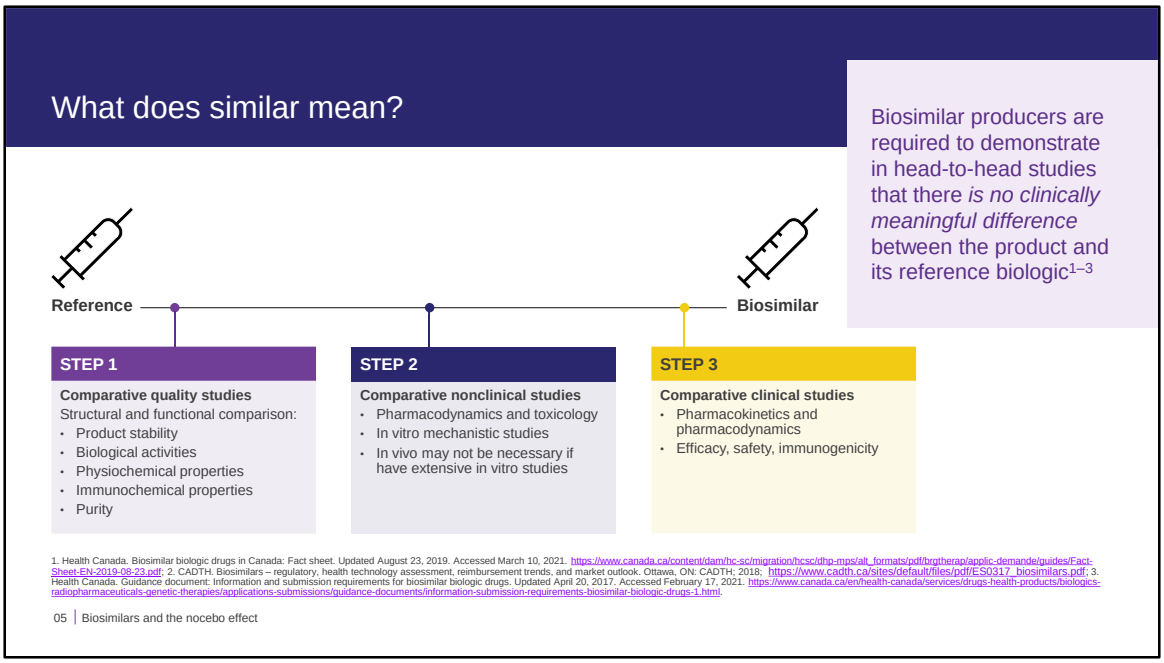




Minor variability in composition may be allowed for a biosimilar. Here, the sugar structures in a glycoprotein (represented by small blue triangles) show some variation between the reference biologic and the biosimilar, but the protein's amino acid sequence (circles) is unchanged, as is its biological activity.[1]

Reference

1. European Medicines Agency. Biosimilars in the EU: information guide for healthcare professionals. Updated February 10, 2019. Accessed March 10, 2021. https://www.ema. europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf



Rigorous lab and human clinical studies are required to prove there are no meaningful differences in safety between a biosimilar and its reference drug, as authorized for sale by Health Canada.[1]

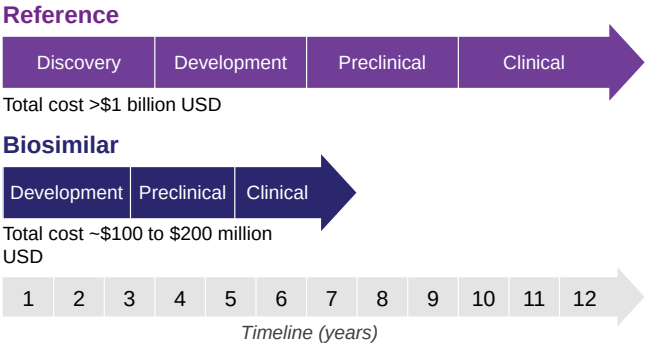
Reference

1. Health Canada. Guidance document: information and submission requirements for biosimilar biologic drugs. Updated April 20, 2017. Accessed February 17, 2021. https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/information-submission-requirements-biosimilar-biologic-drugs-1.html

Biosimilars' shorter timeline means lower costs[1]

Compared to bringing a reference biologic to market, development of a biosimilar is:

- Quicker
- More certain
- Less costly

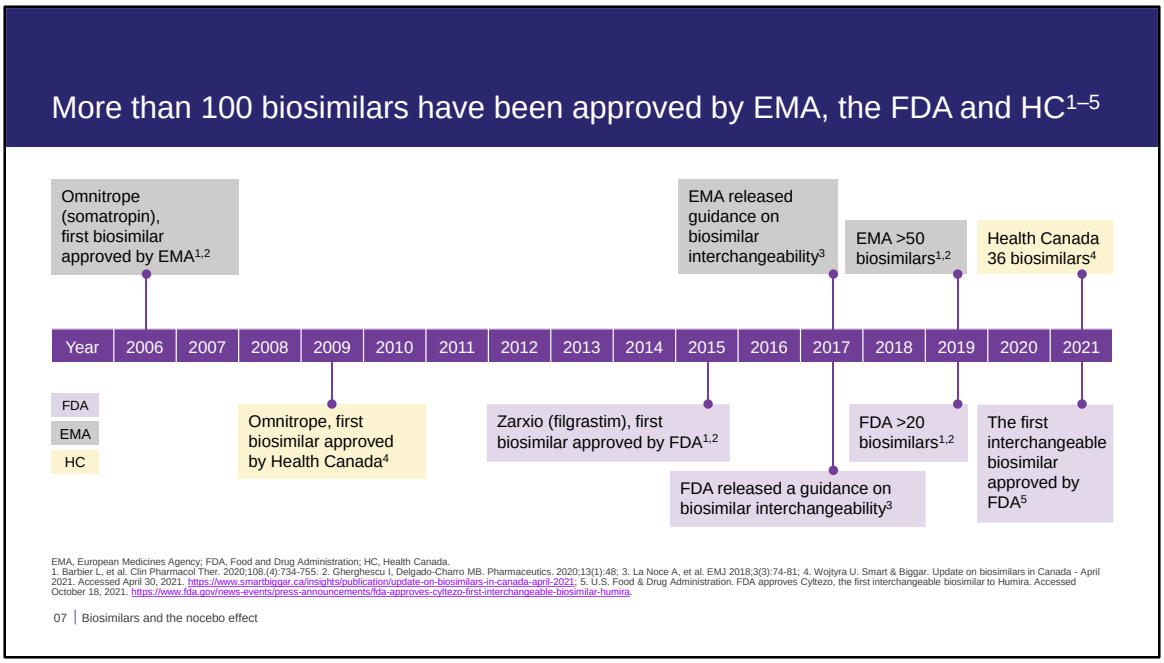


USD, United States Dollar.
1. Agbogbo FK, et al. J Ind Microbiol Biotechnol. 2019;46(9-10):1297-1311.

Biosimilars are less expensive because the cost of developing the drug and getting it approved is shorter, more certain and less costly. A biosimilar does not undergo the drug discovery phase because it is based on an existing drug, and is not required to undergo the initial clinical trial phase to determine effectiveness, because this has already been established by the reference drug.[1]

Reference

1. Agbogbo FK, et al. J Ind Microbiol Biotechnol. 2019;46(9-10):1297-1311.



In Canada, the term "interchangeability" often refers to the ability of a patient to be changed from one drug to another equivalent drug, by a pharmacist, without the intervention of the original prescriber. Health Canada's authorization of a biosimilar is not a declaration of equivalence to the reference biologic drug. The authority to declare two products interchangeable rests with each province and territory according to its own rules and regulations.

Reference

1. Health Canada. Biosimilar biologic drugs in Canada: Fact Sheet. Accessed February 1, 2022. https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html#a16.

In a systematic review, 167 studies showed no differences in safety, efficacy or immunogenicity[1*]

In a systemic review of **178 studies**, a total of **21 000 switched patients** were observed from randomized controlled trials, open-label extension and real-world evidence studies

Switch studies were identified for somatropin, epoetin, filgrastim, insulin, anti-TNFs (adalimumab, etanercept, infliximab), follitropin, and monoclonal antibodies used in oncology (rituximab and trastuzumab)

Based on the conclusion of the authors, the majority of the studies did not identify efficacy, safety or immunogenicity issues as a result of switching from a reference product to its biosimilar version

*Percentage of studies was calculated based on the conclusions of switch studies summarized in the manuscript
TNF; tumour necrosis factor.
1. Barbier L, et al. Clin Pharmacol Ther. 2020;108.(4):734-755.

Note: The review paper did not summarize the number of studies that indicated there were no safety/efficacy/immunogenicity issues. Therefore, this value (93.8%) was determined by reading the conclusions of the switch studies in the supplemental tables and the results section of the manuscript.

EXAMPLE

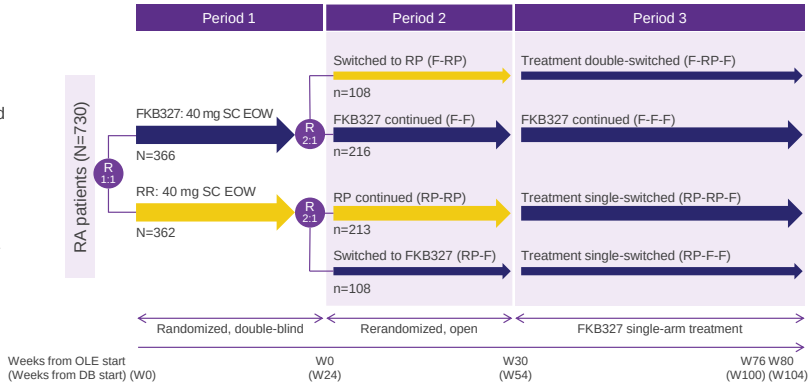
Biosimilar FKB327 has similar efficacy, safety and immunogenicity to reference adalimumab[1]

- Adalimumab is a TNFi
- Phase 3 study of patients with active RA inadequately controlled with methotrexate:

  Period 1: randomized 1:1 to biosimilar or reference product

  Period 2: randomized 2:1 to continue treatment from Period 1 or to switch to the alternative

  Period 3: all received FKB327, forming **four study groups**



DB, double-blind; EOW, every other week; F, FKB327; OLE, open-label extension; RA, rheumatoid arthritis; RP, reference product; SC, subcutaneous; TNFi, tumour necrosis factor inhibitor.

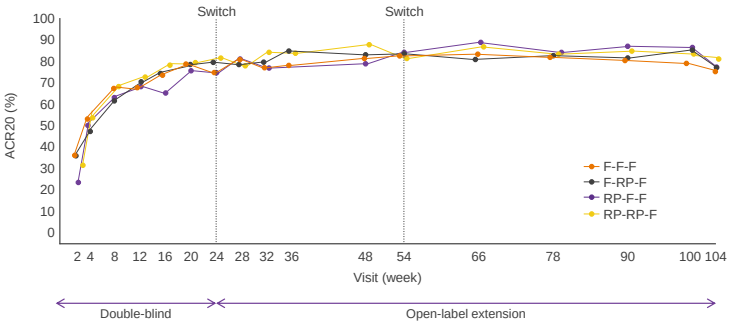
1. Genovese MC *et al*. RMD open. 2020;6(1):e000987.

The next few slides show examples of studies showcasing similar efficacy, safety and immunogenicity for biosimilar vs. reference drugs.

EXAMPLE

Biosimilar FKB327 has similar efficacy, safety and immunogenicity to reference adalimumab[1] (cont'd)

Long-term efficacy results from Weeks 0 to 104*



ACR20 response rates were similar between all four treatment groups

No effect of switching treatments in Period 2 or double switching treatments in Period 3

Switching treatment from reference product to FKB327 or vice versa was not associated with discernible influence of ADA response

*From start of double-blind period of the study
ACR20, American College of Rheumatology 20; ADA, antidrug antibody; F, FKB327; RP, reference product.
1. Genovese MC, et al. RMD open. 2020;6(1):e000987.

- Efficacy endpoints included ACR20/50/70[1]
- Safety was monitored throughout the study by evaluating the incidence of treatment emergent AEs (TEAEs) and AEs of special interest (e.g., infections)[1]
- Immunogenicity was assessed by evaluation of antidrug antibodies (ADAs) by single-assay approach

Reference

1. Genovese MC, et al. RMD open. 2020;6(1):e000987.

EXAMPLE

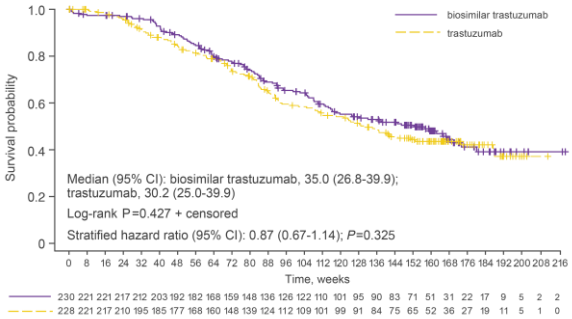
Overall survival between biosimilar trastuzumab and reference trastuzumab groups was comparable (HERITAGE)[1]

Trastuzumab is a humanized IgG1 monoclonal antibody directed against HER2

Phase 3 trial compared median overall survival of patients with HER2-positive metastatic breast cancer treated with biosimilar trastuzumab or trastuzumab

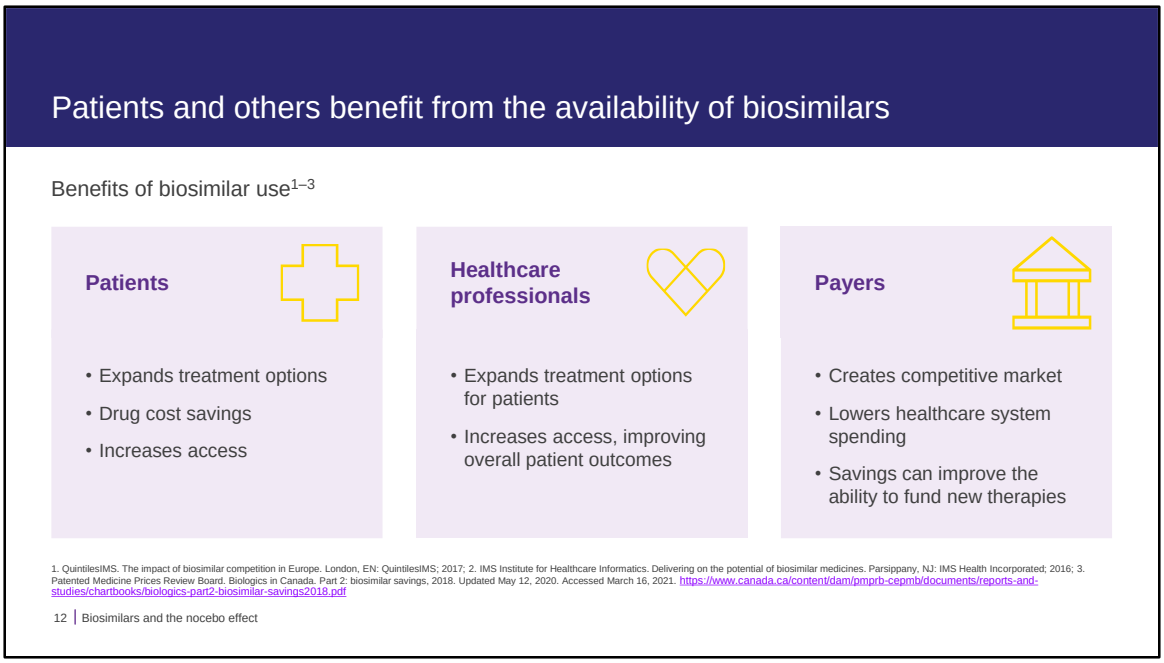
- At the time of analysis at 36 months, median overall survival was 35.0 and 30.2 months between the two treatment groups, respectively

No notable differences in safety between the two treatment groups in incidence or severity of TEAEs



Kaplan-Meier survival curves did not significantly differ between the two treatment groups (P=0.427)

CI, confidence interval; ER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin 1; TEAE, treatment-emergent adverse event.
1. Rugo HS, et al. Breast Cancer Res Treat. 2021:188(2):369-377.



Patients, healthcare professionals and payers like the government all benefit from the cost savings of biosimilars. Lower cost reduces barriers and improves access to treatments for patients. Better access improves the overall health and well-being of the community, which is a goal of healthcare professionals. Healthcare system savings can be used by payers to fund other therapies.[1–3]

References

1. QuintilesIMS. The impact of biosimilar competition in Europe. London, EN: QuintilesIMS; 2017.
2. MS Institute for Healthcare Informatics. Delivering on the potential of biosimilar medicines. Parsippany, NJ: IMS Health Incorporated; 2016.
3. Patented Medicine Prices Review Board. Biologics in Canada. Part 2: biosimilar savings, 2018. Updated May 12, 2020. Accessed March 16, 2021. https://www.canada.ca/content/dam/pmprb-cepmb/documents/reports-and-studies/chartbooks/biologics-part2-biosimilar-savings2018.pdf

The nocebo effect in biosimilar therapy

Low expectations for biosimilars produce poor outcomes: The nocebo effect[1]

The words placebo and nocebo are derived from Latin: *placere* (to please) and *nocere* (to harm)

Placebo and nocebo refer to effects that people experience specifically because of their expectations that those treatments will help or harm them

1. Best Practice Advocacy Centre New Zealand. Updated August 30, 2019. Accessed October 2021. The nocebo effect: what is it, why is it important and how can it be reduced? https://bpac.org.nz/2019/nocebo.aspx.

Transitioning from a reference biologic to its biosimilar is associated with the potential for a “nocebo” effect.

Patients' psychological biases can lead to poorer outcomes with biosimilars[1–3]

Learning and conditioning

- Previous negative experience or unsuccessful treatment
- Observing or hearing about another person's side effects

Contextual factors

- Lower cost and limited choice of medication

Negative expectations

- Awareness of reported side effects
- Negative impression of the medication
- Media or internet reports

Misattribution

- Association of treatment with common daily symptoms

NOCEBO EFFECT

Patient experiences reduced efficacy or attributes adverse events to the biosimilar

1. Colloca L, et al. Front Pharmacol. 2019;10:1372; 2. Colloca L, Barsky AJ. N Engl J Med. 2020;382:554-561; 3. Petrie KJ, Reif W. Ann Rev Psychol. 2019;70;599-625.

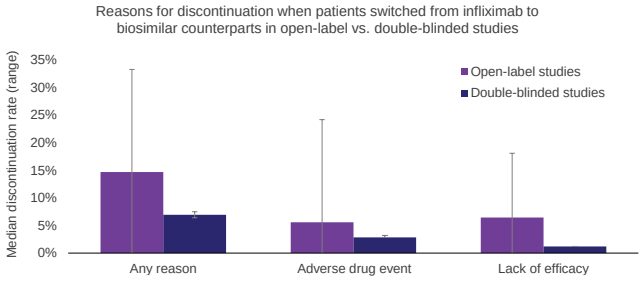
Patients' negative expectations affect their willingness to remain on a biosimilar[1]

In a systematic review of **31 studies**, 28 involved switches from **infliximab** and 3 from **etanercept** to their biosimilar product counterparts

Higher discontinuation rates were found in **open-label studies** compared to **double-blinded studies** for both biologics due to **adverse drug events**

For infliximab, discontinuation rates were also higher among **open-label trials** due to **any reason** or **lack of efficacy**

- **In open-label studies, where patients know they are on a biosimilar, discontinuation rates are ~ two-fold higher than in blinded studies of the same comparison**



1. Odinet JS, et al. J Manag Care Spec Pharm. 2018;24:952-959.

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The researchers found higher discontinuation rates for any reason, adverse events, and lack of efficacy in biosimilar infliximab open-label studies vs. double-blind studies, suggesting that nocebo effects may inhibit the adoption of this biosimilar.[1]

Reference

1. Odinet JS, et al. J Manag Care Spec Pharm. 2018;24:952-959.

Patient-unfriendly language in packaging may produce a nocebo effect: Study design

Objective

- To assess the different package information leaflets (PILs)
- To assess whether PILs could influence the nocebo effect

Study design

- 100 patients undergoing orthopedic surgery in a three-arm (1:1:1 allocation ratio) parallel randomized controlled pilot trial
- Received only ibuprofen 600 mg for pain relief after discharge

DEPICTION OF ADVERSE EVENTS

Simplified language

Adverse events

Gastrointestinal conditions

Ibuprofen caused stomach and bowel discomfort in about 1 in 100 people

99 out of 100 people did not have stomach or bowel discomfort from ibuprofen

Serious (rare) adverse events

Some people reported other problems while taking ibuprofen. There is some evidence suggesting that ibuprofen may be connected to stomach or bowel bleeding, ulcers or perforations, and severe (in rare cases life-threatening) skin reactions. But there are no good studies that provide information on the frequency of these side effects.

Standard language

Adverse events

For the evaluation of adverse events, the following scheme is used:

Very often: more than 1 in 10 patients
Often: 1 to 10 patients in 100
Occasional: 1 to 10 patients in 1000
Rare: 1 to 10 patients in 10 000
Very rare: less than 1% in 10 000
Unknown: frequencies unknown because of availability of data

Disease of the gastrointestinal system:

Very often: gastrointestinal conditions such as heartburn, stomach ache, nausea, vomiting, flatulence, diarrhea and obstipation

Serious (rare) adverse events

Often: gastric/duodenal ulcer (peptic ulcer) under circumstances with bleeding and rupture, stomatitis with ulcer (ulcerative stomatitis), potentiation of ulcerative colitis or Crohn's disease

Occasional: gastritis

Very rare: esophagitis and pancreatitis, intestinal diaphragmatic narrowing

1. Prediger B, et al. Trials. 2019;20(1):458.

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Three groups[1]:

Simplified PIL: The main design criteria were comprehensibility and descriptions that avoided incorrect risk perception on AEs.

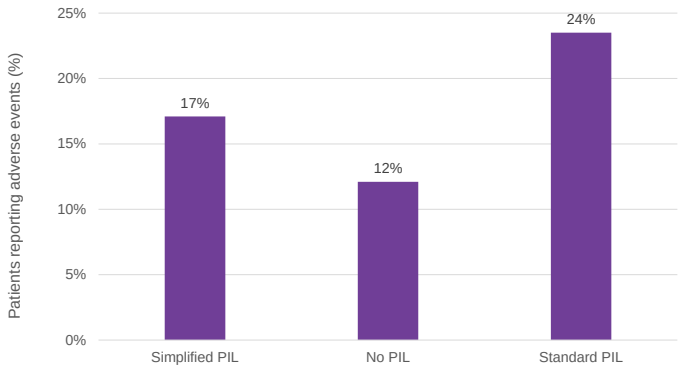
- Written in plain language
- AEs were reported with a focus on avoiding biased risk perception
  - Standard PIL
  - No PIL

Reference

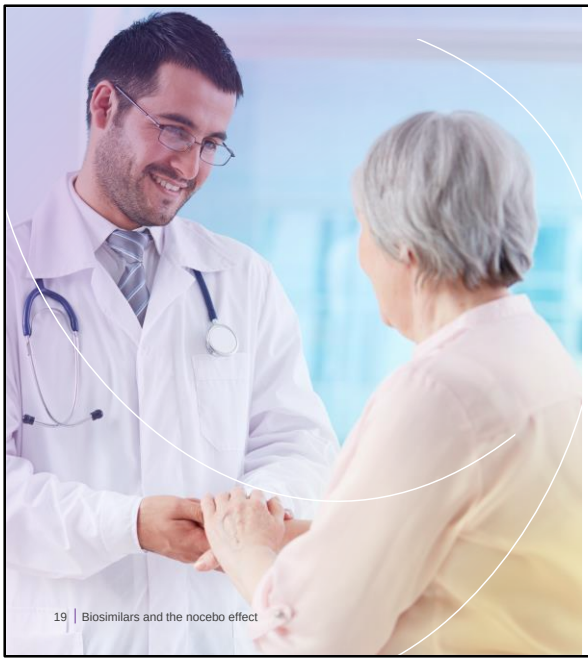
1. Prediger B, et al. Trials. 2019;20:1-10.

Patient-unfriendly language in packaging may produce a nocebo effect

This small study showed a **trend toward greater prevalence of AEs** when patients viewed AE information in standard medical language, compared with patient-friendly language or no packaging information



AE, adverse event; PIL, package information leaflet.
1. Prediger B, et al. Trials. 2019;20(1):458.



Healthcare professionals can help minimize the nocebo effect[1]

To improve outcomes for patients transitioning to biosimilars

- Emphasize that biosimilars are as safe and effective as other biologics
- Describe treatment benefits and risks
- Focus on positive attributes
- Avoid negative phrases
- Explore patients' possible negative treatment history
- Allow time for patients to ask questions

1. Best Practice Advocacy Centre New Zealand. The nocebo effect: what is it, why is it important and how can it be reduced? Updated August 30, 2019. Accessed October 2021. https://bpac.org.nz/2019/nocebo.aspx.

Passive strategies to reduce the occurrence of the nocebo effect during a patient consultation[1,2]

Use positive nonverbal cues

- Caring, empathetic attitude
- Eye contact, smiling, affirmative head nods/gestures

Recognize risk factors

- Anxiety
- Pessimism
- History of unexplained symptoms
- Habit of searching for medical information

1. Colloca L, et al. Front Pharmacol. 2019;10:1372; 2. Colloca L, Barsky AJ. N Engl J Med. 2020;382:554-561.

Active strategies to reduce the occurrence of the nocebo effect during a patient consultation[1,2]

Reassure to alleviate any anxiety

- Present the patient with possible outcomes of the treatment
- Reassure patients that they can contact you if any questions or concerns arise

Alignment using open dialogue

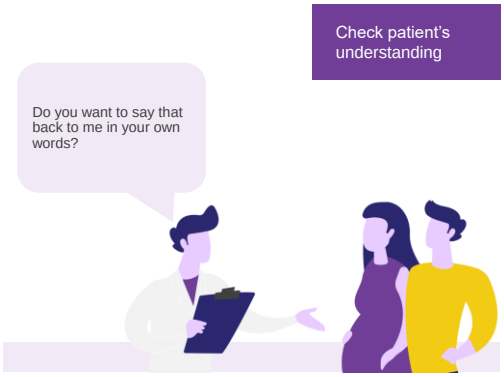
- Check the patients' understanding about biosimilars
- Fill in patients' knowledge gaps to reduce uncertainty and anxiety
- Leave enough time to answer questions and discuss concerns
- Describe other patients who benefited from the biosimilars

Frame the discussion carefully

- Phrase information positively
- Focus on the majority of patients who do not experience a side effect

1. Colloca L, et al. Front Pharmacol. 2019;10:1372; 2. Colloca L, Barsky AJ. N Engl J Med. 2020;382;554-561.

Reassure the patient to alleviate any anxiety[1]

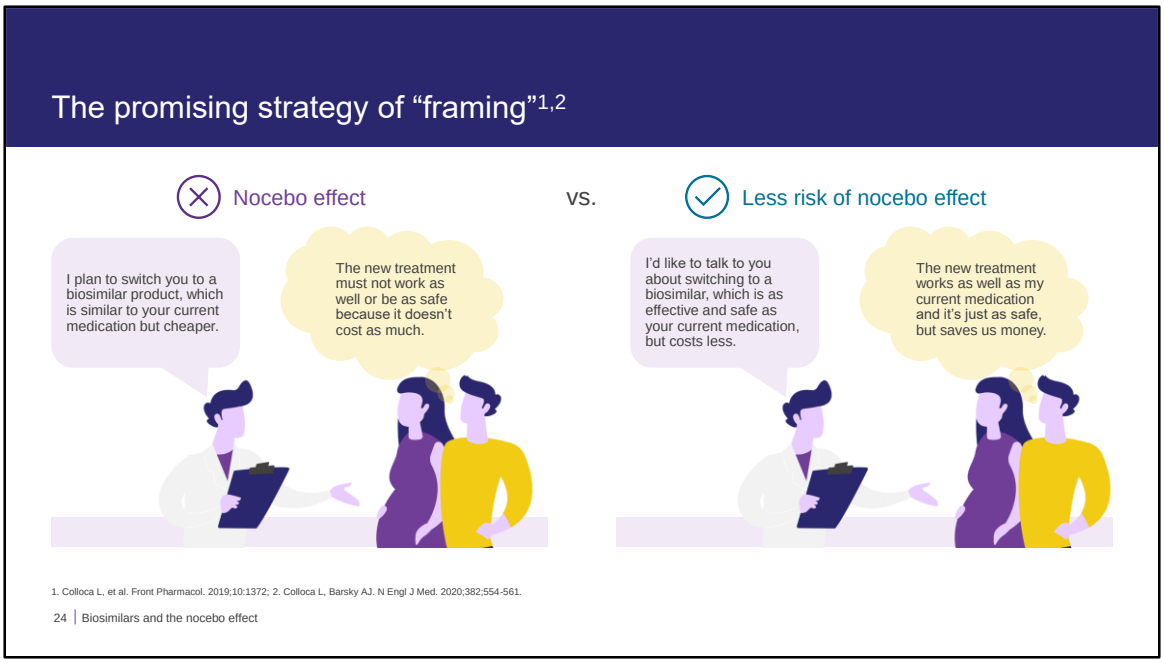


1. Best Practice Advocacy Centre New Zealand. Updated August 30, 2019. Accessed October 2021. The nocebo effect: what is it, why is it important and how can it be reduced? https://bpac.org.nz/2019/nocebo.aspx.

Alignment using open dialogue[1]

This approach helps mitigate nocebo effects by allowing patients to feel more in control of their treatment

1. Best Practice Advocacy Centre New Zealand. Updated August 30, 2019. Accessed October 2021. The nocebo effect: what is it, why is it important and how can it be reduced? https://bpac.org.nz/2019/nocebo.aspx.

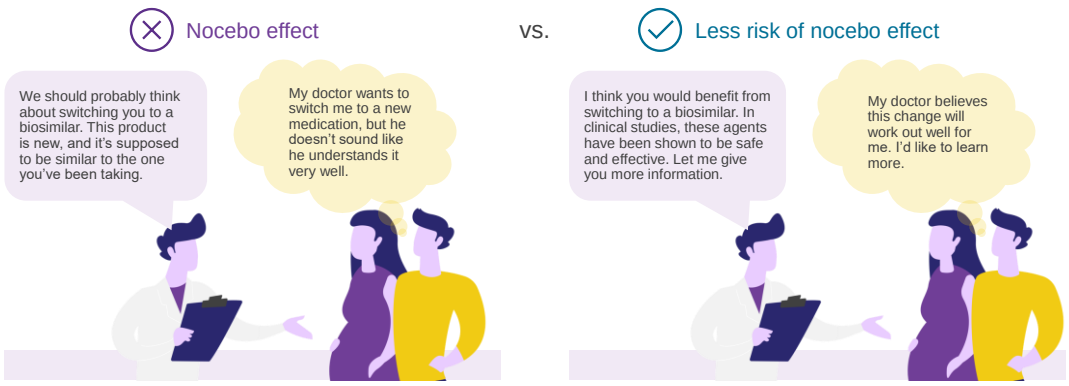


A possible strategy to reduce the incidence of the nocebo effect and improve drug adherence, while continuing to provide accurate details about the benefits and risks of a drug through informed consent, would be to phrase information positively. Instead of focusing the conversation on the percentage of people who experienced negative outcomes, present the same information with a focus on those who experienced positive outcomes.

References

1. Colloca L, et al. Front Pharmacol. 2019;10:1372.
2. Colloca L, et al. N Engl J Med. 2020;382;554-561.

The promising strategy of "framing"[1,2] (cont'd)



1. Colloca L, et al. Front Pharmacol. 2019;10:1372; 2. Colloca L, Barsky AJ. N Engl J Med. 2020;382:554-561.

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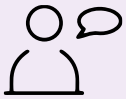
References

1. Colloca L, et al. Front Pharmacol. 2019;10:1372.
2. Colloca L, et al. N Engl J Med. 2020;382;554-561.

Preparation before patient consultation results in minimizing the occurrence of the nocebo effect

Educate yourself on the topic of biosimilars



Be ready to explain biosimilars to your patients

Understand the nocebo effect and how it can influence biosimilar adherence

Know where to find additional resources

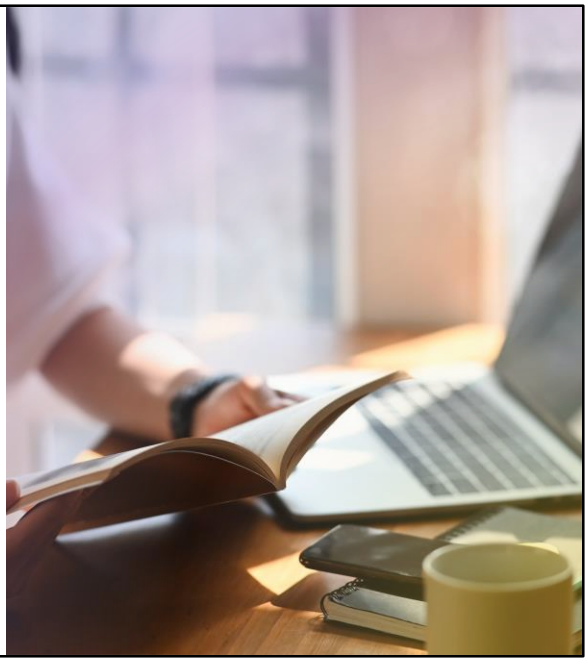
Healthcare professionals play a key role in reducing the incidence of nocebo effects and thus improving patient outcomes.

Summary

- There are **no clinically meaningful differences** between a biosimilar and its reference biologic
- Current switch studies indicate no safety, efficacy or immunogenicity issues
- The **nocebo effect** seems to play a role in setting up patients for nonoptimal outcomes. In switch studies:
  - **Overall discontinuation** rates were higher in **open-label** vs. **double-blind** studies
  - These additional discontinuations were attributed to both **adverse events** and a reported **lack of efficacy**
- The **nocebo effect** might prevent the widespread uptake of biosimilars
- HCPs should recognize patients who are more **susceptible to nocebo responses**
- Language matters; positive framing is a potentially promising method to prevent the **nocebo effect**
- HCPs should **educate themselves** on the topic of biosimilars and be ready to **explain biosimilars to patients**
- HCPs can use passive and active strategies to help **minimize the nocebo effect**

HCP; healthcare professional.

Further reading



Helpful resources

Health Canada:
https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/biosimilar-biologic-drugs.html

European Medicines Agency (EMA):
https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview

United States Food and Drug Administration (FDA):
https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars

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1. Agbogbo FK, Ecker DM, Farrand A, et al. Current perspectives on biosimilars. J Ind Microbiol Biotechnol. 2019;46(9-10):1297-1311.
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3. Best Practice Advocacy Centre New Zealand. The nocebo effect: what is it, why is it important and how can it be reduced? Updated August 30, 2019. Accessed October 2021.https://bpac.org.nz/2019/nocebo.aspx
4. CADTH. Biosimilars – regulatory, health technology assessment, reimbursement trends, and market outlook. Ottawa, ON: CADTH; 2018. https://www.cadth.ca/sites/default/files/pdf/ES0317_biosimilars.pdf
5. Colloca L, Panaccione R, Murphy TK. The Clinical Implications of Nocebo Effects for Biosimilar Therapy. Front Pharmacol. 2019;10:1372.
6. Colloca L, Barsky AJ. Placebo and nocebo effects. N Engl J Med. 2020;382:554-561.
7. European Medicines Agency. Biosimilars in the EU: Information guide for healthcare professionals. Updated February 10, 2019. Accessed March 10, 2021. https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf
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9. Gherghescu I, Delgado-Charro MB. The Biosimilar Landscape: An Overview of Regulatory Approvals by the EMA and FDA. Pharmaceutics. 2020;13(1):48.
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12. La Noce A, Ernst M. Switching from reference to biosimilar products: An overview of the European approach and real-world experience so far. EMJ 2018;3(3):74-81.
13. Odinet JS, Day CE, Cruz JL. The biosimilar nocebo effect? A systematic review of double-blinded versus open-label studies. J Manag Care Spec Pharm. 2018;24.10:952-959.
14. Prediger B, Meyer E, Büchter R, et al. Nocebo effects of a simplified package leaflet compared to unstandardised oral information and a standard package leaflet: a pilot randomised controlled trial. Trials. 2019;20(1):458.
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16. Petrie KJ, Reif W. Psychobiological mechanisms of placebo and nocebo effects: pathways to improve treatments and reduce side effects. Ann Rev Psychol. 2019;70;599-625.
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