Making the Switch from Biologics to Biosimilars in IBD: Knowledge Over Skepticism

This activity is supported by educational funding provided by Amgen

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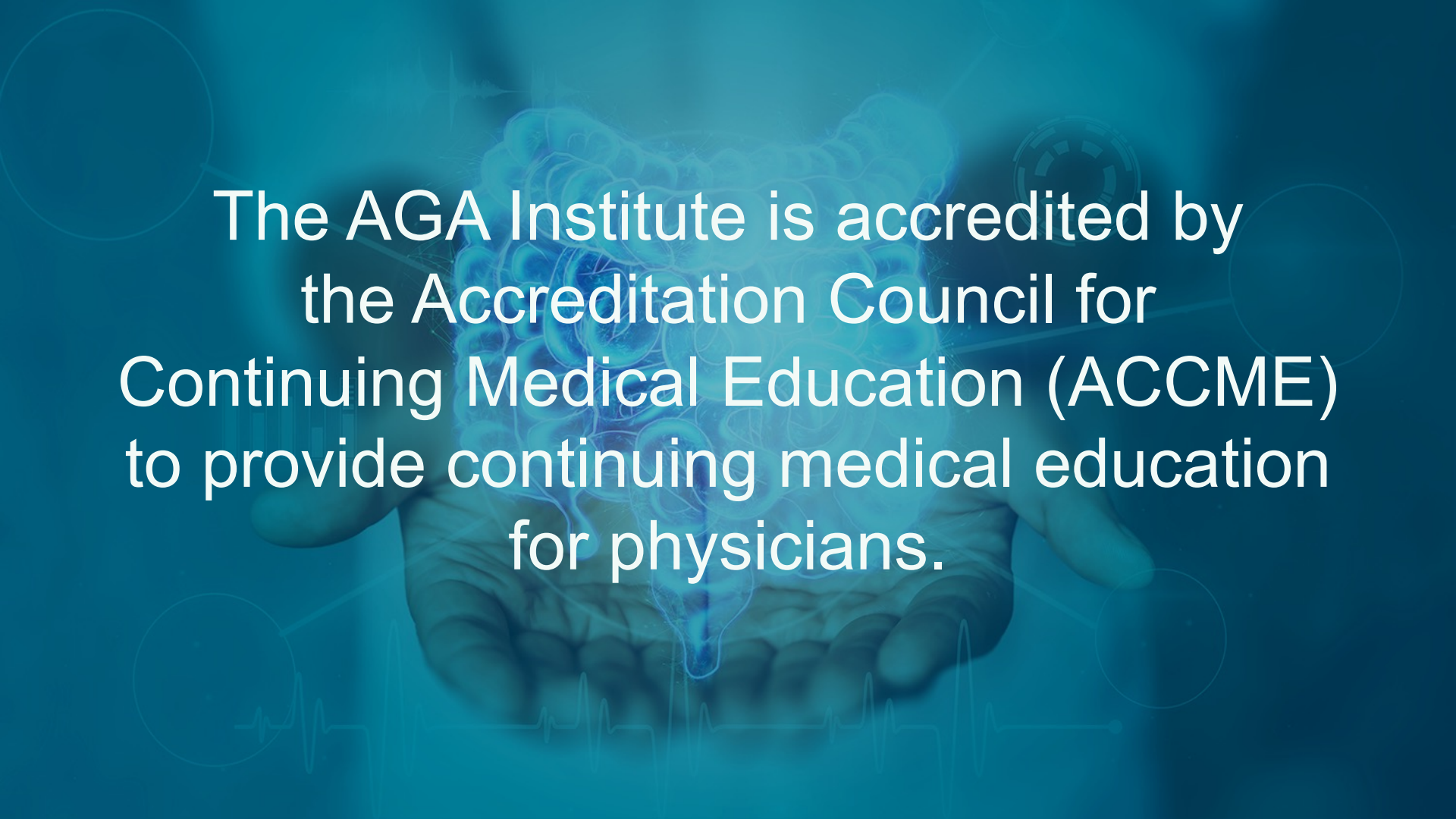
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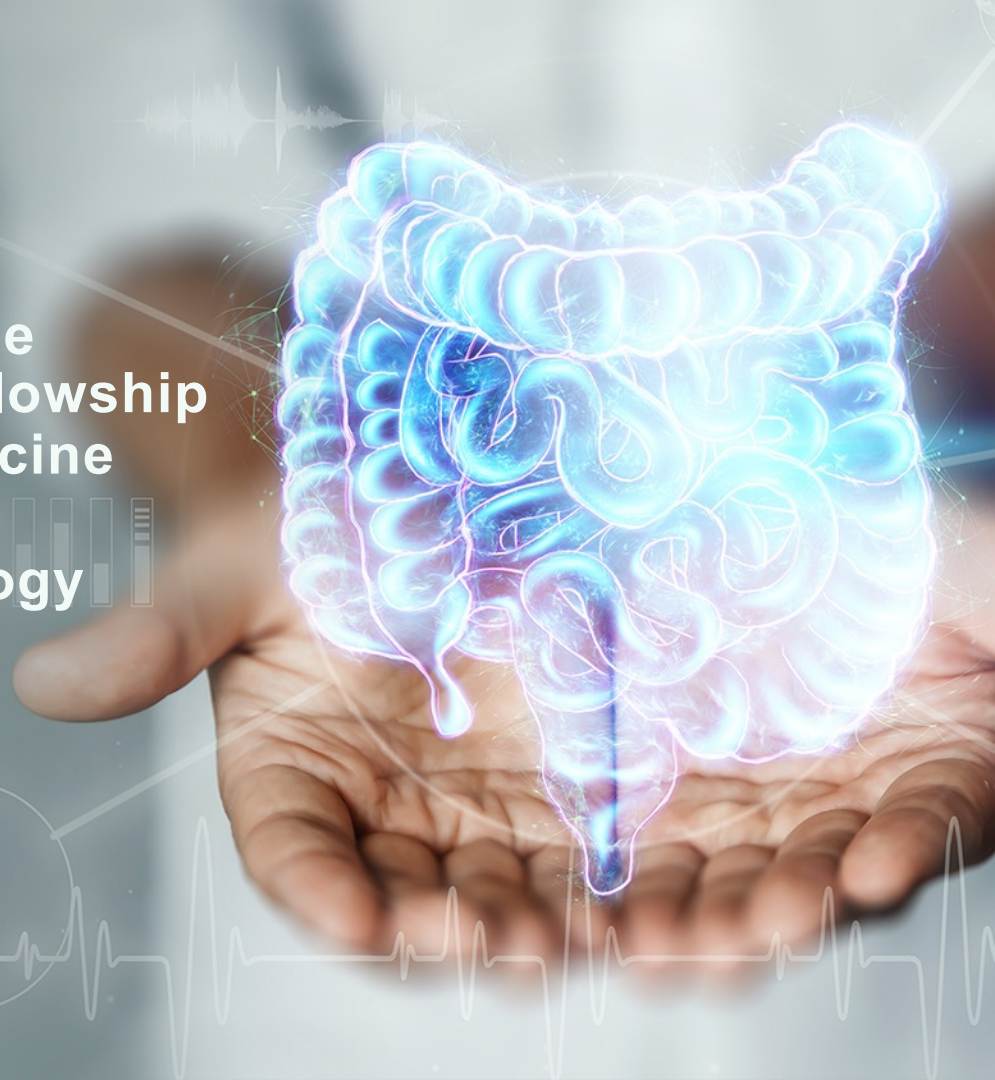
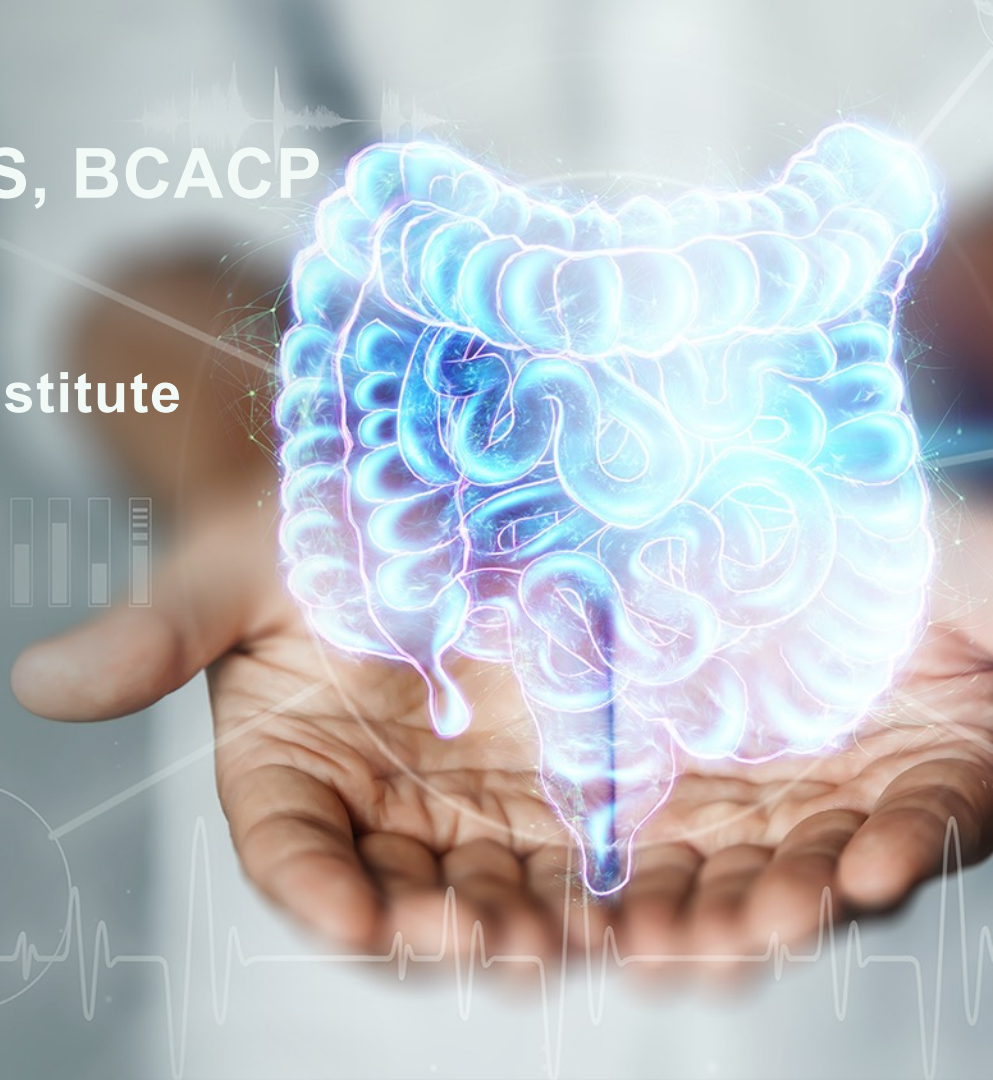
Edward V. Loftus, Jr., MD

Professor of Medicine
Mayo Clinic College of Medicine
Co-Director, Advanced IBD Fellowship
Mayo Graduate School of Medicine
Consultant, Division of
Gastroenterology and Hepatology
Mayo Clinic
Rochester, MN



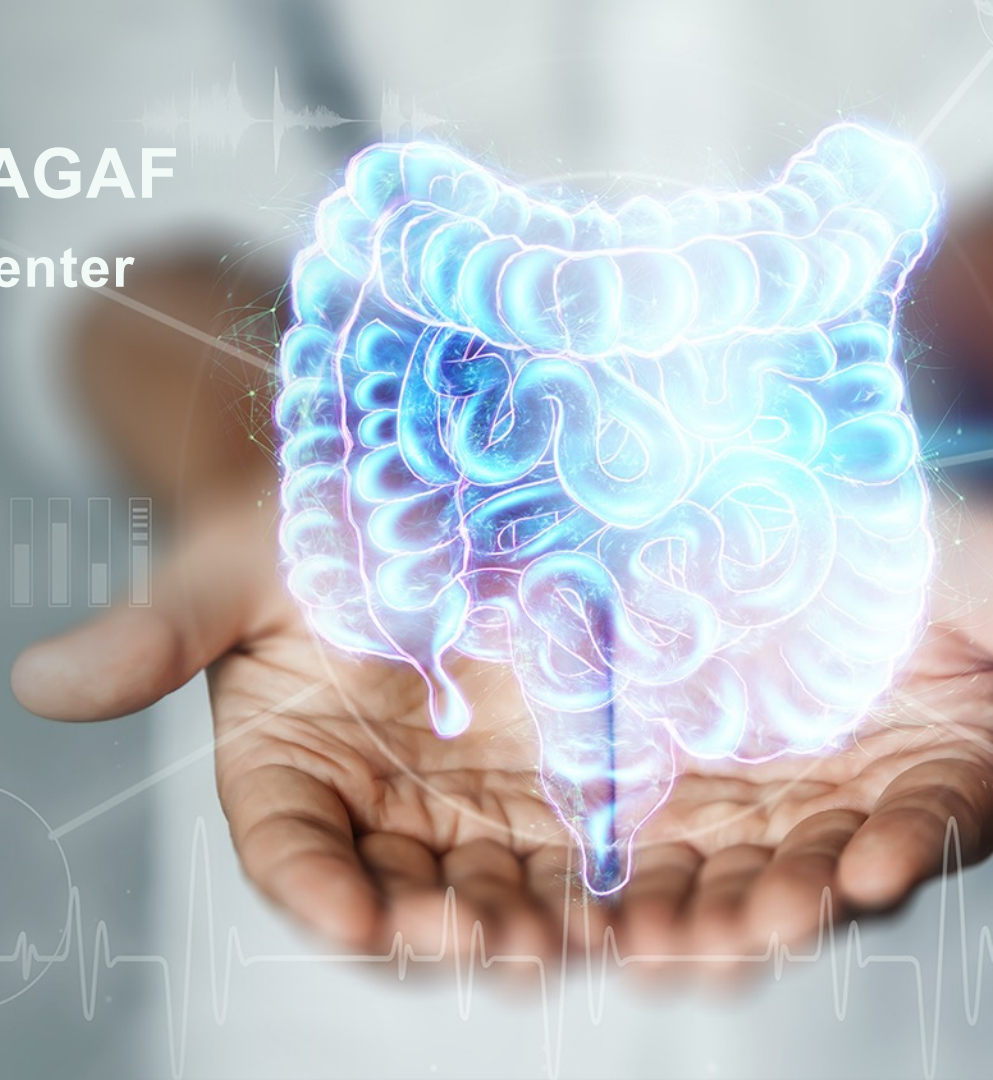
Shubha Bhat, PharmD, MS, BCACP

Clinical Pharmacy Specialist,
Gastroenterology
Digestive Disease & Surgery Institute
Cleveland Clinic
Cleveland, OH



Christina Ha, MD, FACG, AGAF

Inflammatory Bowel Disease Center
Mayo Clinic
Scottsdale, AZ



Define terminology related to biosimilar products, including interchangeability, substitution, and switching.

LEARNING OBJECTIVE 1

Audience Response

Extrapolation with biosimilars requires which of the following?

A. At least one clinical study of the biosimilar is required
B. No clinical study of the biosimilar is required
C. The reference drug is available as a generic
D. The efficacy is less than the reference drug
E. I don’t know

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Definitions

- **Reference product**
  Also called “originator product”; approval based on full complement of safety and effectiveness data
- **Biosimilar product**
  Product is “highly similar” to reference product and has no clinically meaningful variations in terms of safety, efficacy, purity, and potency
- **Interchangeable product**
  Meets additional requirements outlined by the Biologics Price Competition and Innovation (BPCI) Act (including efficacy and safety with switching)
  The pharmacist/specialty pharmacy can dispense biosimilar vs. branded version (or vice versa) without intervention by the prescriber under BPCI Act*

Reference Product
A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared

Biosimilar Product
A biosimilar is a biological product that is highly similar and has no clinically meaningful differences from an existing FDA-approved reference product

Interchangeable Product
An interchangeable product is a biosimilar product that meets additional requirements

*this is state dependent and can differ by state

U.S. Food and Drug Administration (FDA) Website. 2017. www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products. Accessed January 20, 2022. FDA Website. www.fda.gov/media/108557/download. Accessed January 20, 2022. Kaida-Yip F, et al. *World J Clin Cases.* 2018;6(8):161-166.

Definitions

Equivalence

- The proposed product is not inferior to, nor is it superior to, the index product

Extrapolation

- May be approved for other indications of the reference product without additional studies

Substitution

- Pharmacist dispenses interchangeable biosimilar in place of reference product, unless prohibited by the prescriber

Switching

- Physician prescribes a biosimilar in place of approved originator product

FDA Website. 2017. www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products. Accessed January 20, 2022

Biosimilars: FDA Definitions and Requirements

- A biological product that is ***HIGHLY similar*** to the reference product with only **MINOR** differences in ***clinically inactive*** components
- No **CLINICALLY MEANINGFUL DIFFERENCE** between the biological product and the reference product in terms of safety, purity and potency

Like fingerprints from identical twins,
biosimilars are highly similar to the originator reference product but not identical

FDA Website. FDA Biologics Price Competition and Innovation Act of 2009. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/implementation-biologics-price-competition-and-innovation-act-2009.

Generics, Second-Generation, and Biosimilars: More Different Than Similar

Generic Drugs

- Small-molecule drugs that are less complex than biosimilars
- Manufacturing process is several orders of magnitude less complex; about 50 QA tests done before approval
- Approximately 3 years to develop
- Regulated under different legislation

Second-Generation (or Biobetter)

- Structurally different from originally licensed drug
- Improves performance while preserving MOA
- Examples:
  - IFX and ADA
  - Filgrastim and pegfilgrastim
- Not a biosimilar

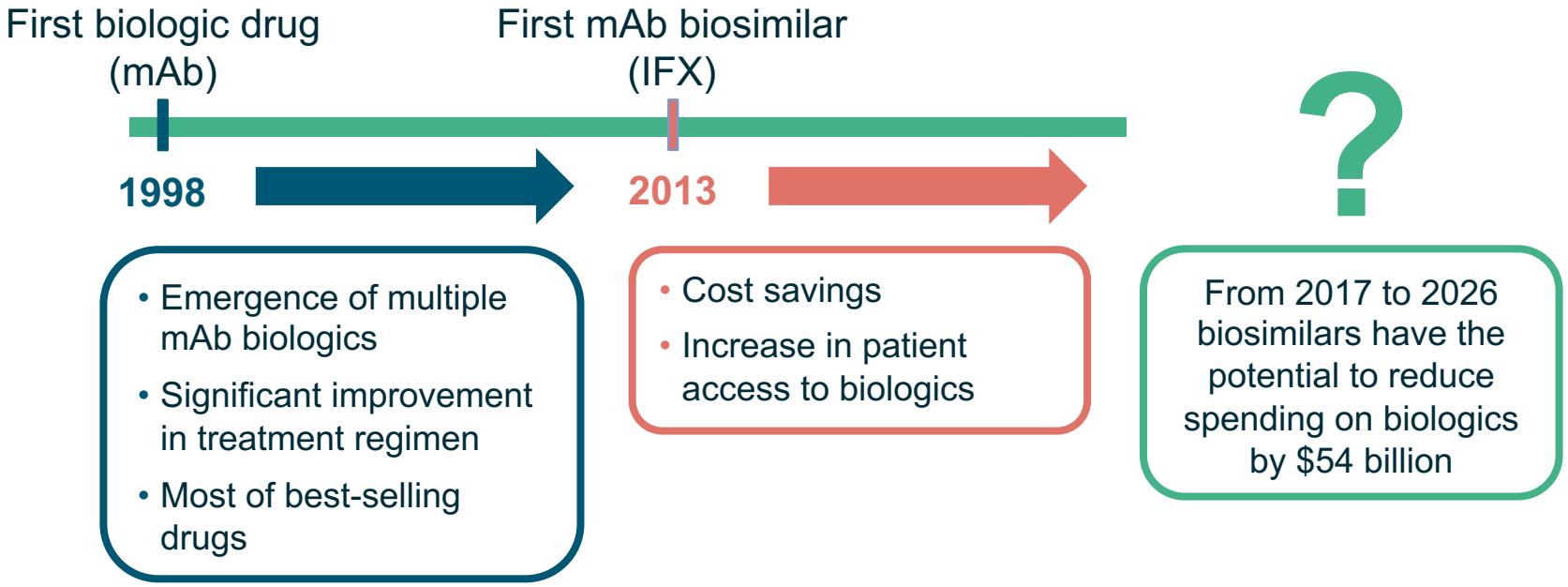
Biosimilars

- Complex structure made up of many ingredients
- Each manufactured in a unique living cell; similar, but not exact, copy can be made
- About 250 QA tests done before possible approval
- Approximately 7 years to develop

ADA = adalimumab; IFX = infliximab; MOA = mechanism of action

Woodcock J, et al. *Nat Rev Drug Discov*. 2007;6(6):437-442. www.aga-resources.com/biologics/hcp_guide/pubData/mobile/index.htm#/1/.

Biosimilars Increase Access to Biologic



mAb = monoclonal antibody

Mulcahy AW, et al. *Rand Health Q*. 2018;7(4):3. Monaco C, et al. *Int Immunol*. 2015;27(1):55-62. Ecker DM, et al. *MAbs*. 2015;7(1):9-14. Philippidis A. Genetic Engineering & Biotechnology News Website. 2018. https://www.genengnews.com/a-lists/the-top-15-best-selling-drugs-of-2017/. Pharmaceutical Technology Website. 2017. https://www.pharmaceutical-technology.com/research-reports/researchreporttop-pharma-forecasted-sales-underestimated-by-analysts-5776867/. Péntek M, et al. *World J Gastoenterol*. 2017;23(34):6294-6305.

Overview of Biosimilar Development Process

Develop highly similar product

Technical development

- **Thorough characterization of the reference** medicine
- State-of-the-art **manufacture of the biosimilar**
- **Match molecular profile** of the biosimilar with the reference medicine (structure and function/biological activity)

Confirm biosimilarity

Preclinical | Phase I | Phase III

- **Demonstrate PD/PK equivalence**
- **Confirm efficacy and safety** via tailored phase III studies
- **Support extrapolation** to non-studied indications
- **Demonstrate no increased risk of immunogenicity** compared to the reference medicine

Totality of the Evidence

PD = pharmacodynamic; PK = pharmacokinetic

Modified from Aapro M, et al. *Ther Adv Med Oncol.* 2018;10:1758835918768419.

Extrapolation of Biosimilar Efficacy and Safety Data

Extrapolation

- Clinical trials in one indication used as rationale for clinical use in other indications for which the originator biological product is approved
- Requires appropriate scientific justification

Extrapolation may be possible if:

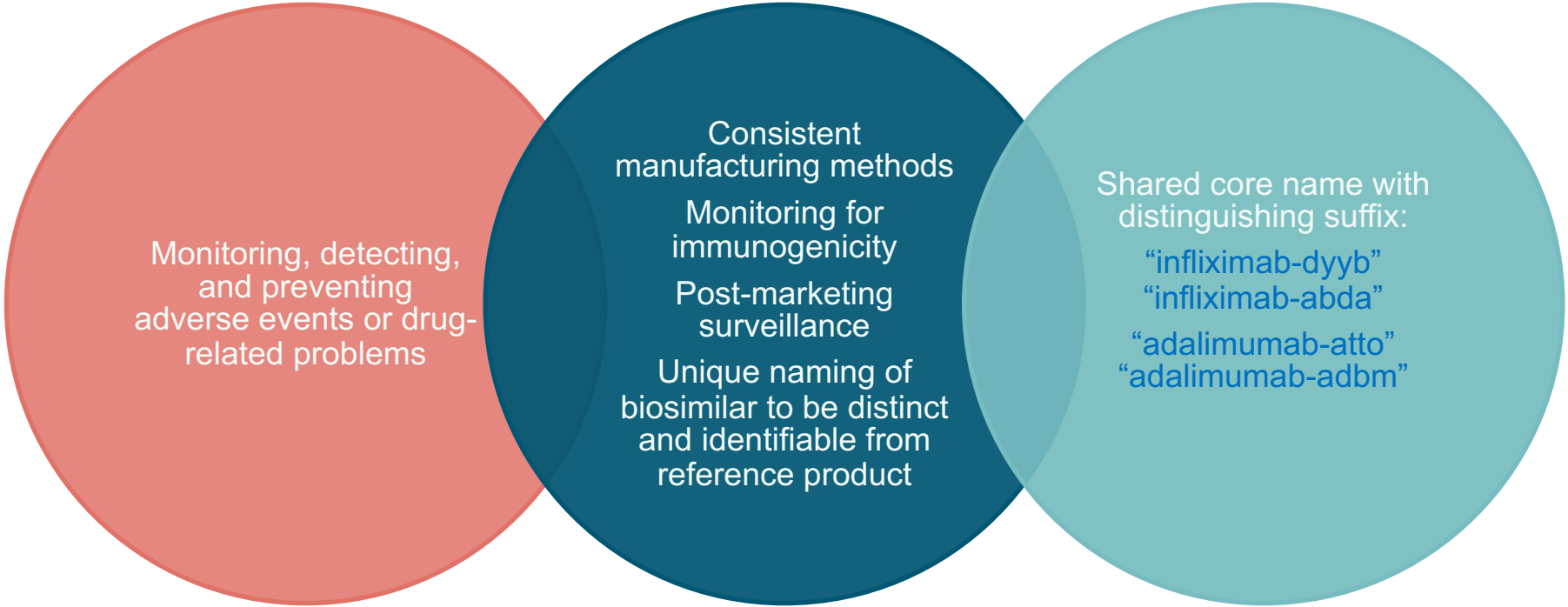
- Overall similarity with originator biological product is demonstrated based on the totality of the evidence
- Clinical similarity is demonstrated in a key indication
- Discussion of product mechanism of action and pathophysiology of the conditions involved supports justification

FDA Website. FDA Biologics Price Competition and Innovation Act of 2009. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/implementation-biologics-price-competition-and-innovation-act-2009. Weise M, et al. *Blood*. 2012;120:5111-5117. FDA Website. 2015. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/scientific-considerations-demonstrating-biosimilarity-reference-product. EMA Website. 2014. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf.

Application to Practice: Clinical Scenarios

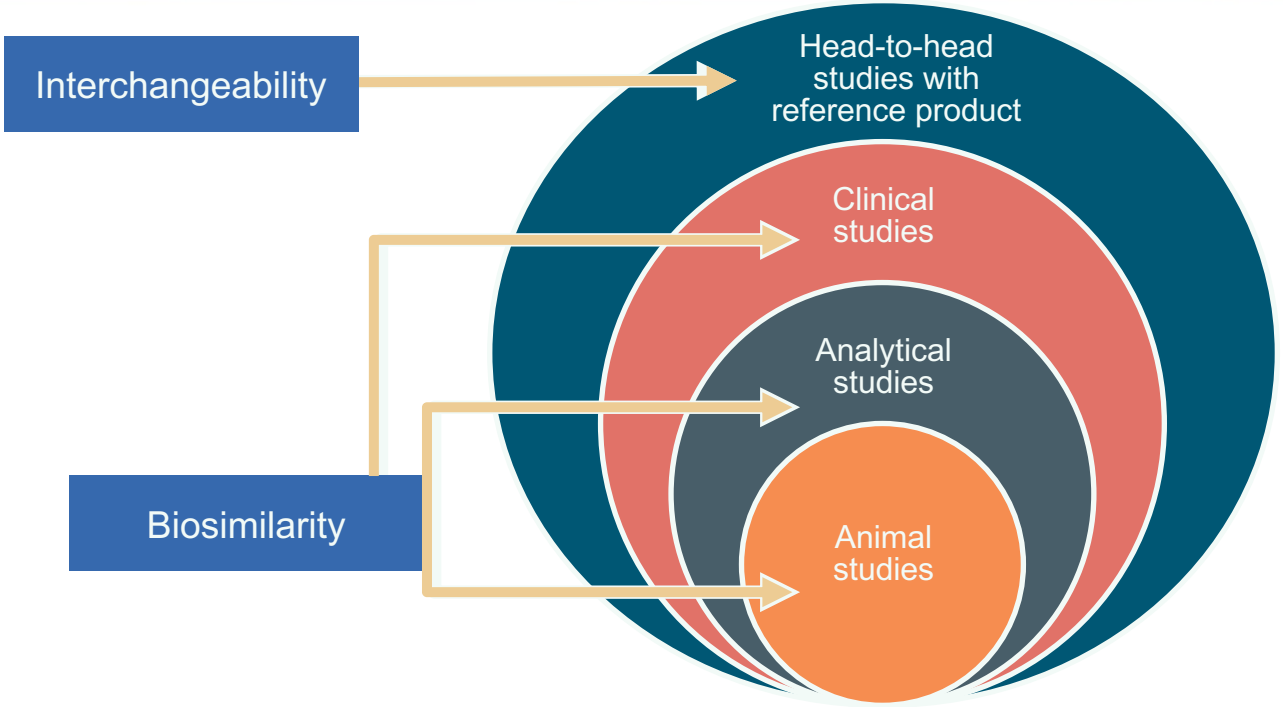
- Your patient, Jessica, has been taking Remicade (reference infliximab) for 14 months
- Her recent labs revealed therapeutic IFX levels
- Jessica recently heard about a new therapy, Avsola (infliximab-axxq), and requests to be put on it but asks if it is safe long-term
- **What will you tell Jessica?**

Post-Marketing Pharmacovigilance



FDA Website. 2020. https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars.

Biosimilar vs. Interchangeable Biosimilar



An interchangeable product **may be substituted** for the reference product **without the intervention of the health care professional** who prescribed the reference product

Lim S. FDA Website. https://www.fda.gov/media/113820/download.

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Audience Response

Extrapolation with biosimilars requires which of the following?

A. At least one clinical study of the biosimilar is required
B. No clinical study of the biosimilar is required
C. The reference drug is available as a generic
D. The efficacy is less than the reference drug
E. I don’t know

CME OUTFITTERS

Assess the efficacy and safety of biosimilars via clinical trial data and real-world evidence in regard to treatment selection for patients with IBD.

LEARNING OBJECTIVE 2

Audience Response

What is the percentage of your patients with inflammatory bowel disease (IBD) who have ever been prescribed a biosimilar?

A. None
B. 1%-24%
C. 25%-49%
D. 50%-74%
E. 75%-100%

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IBD Biosimilars in the United States

Infliximab Biosimilars

Avsola* (infliximab-axxq)
Inflectra* (CT-P13) (infliximab-dyyb)
Renflexis* (infliximab-abda)
Ixifi (infliximab-qbtx)

Adalimumab Biosimilars

Abrilada (adalimumab-afzb)
Amjevita (ABP 501) (adalimumab-atto)
Cyltezo‡ (BI 695501) (adalimumab-adbm)
Hadlima (SB5) (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Hyrimoz (adalimumab-adaz)

…and more to come

*Commercially available in the United States, ‡ = approved by the FDA but not commercially available as of 1/21/21

CME OUTFITTERS

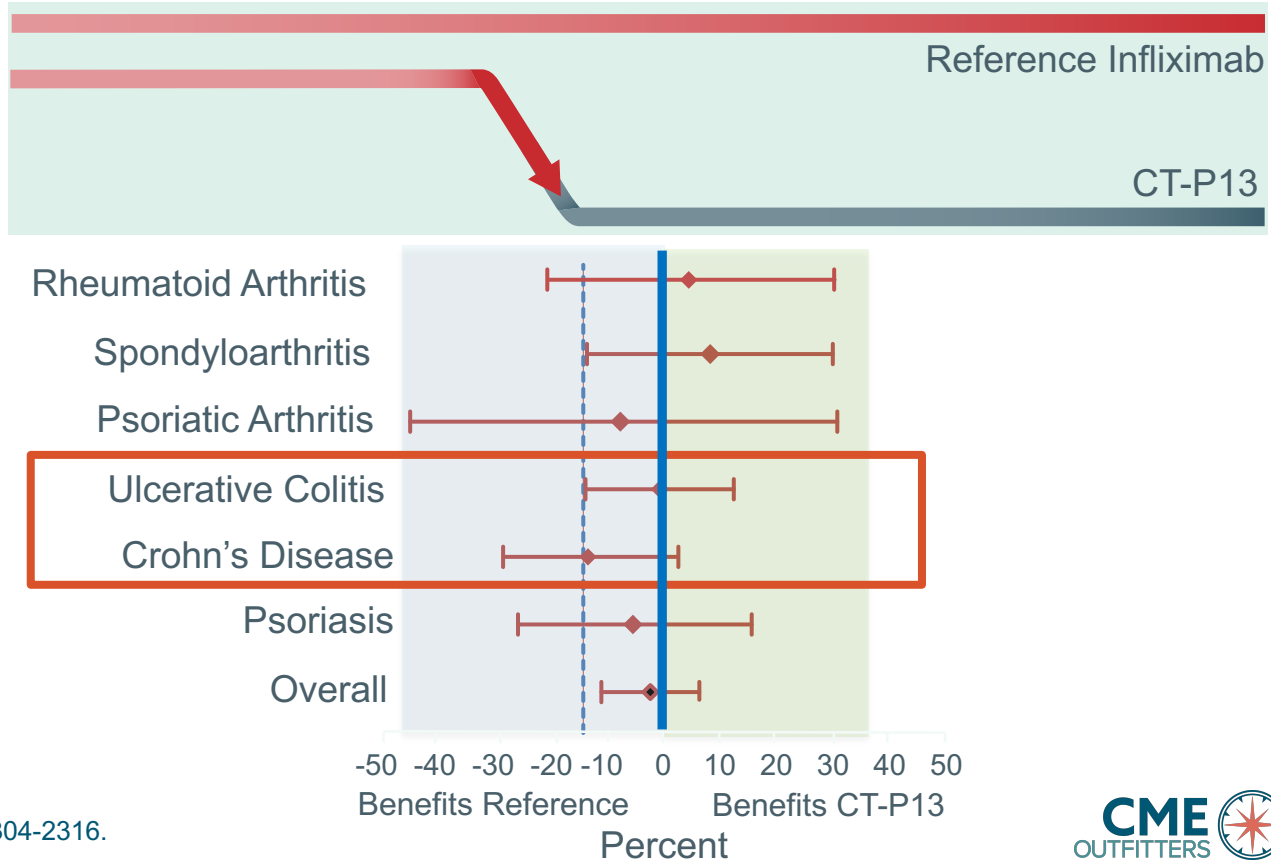
Clinical Trials in IBD

- Disease states used for approval are generally rheumatoid arthritis, psoriasis, and psoriatic arthritis
- Extrapolation of data supports use in other clinical indications
- Currently, open-label studies of biosimilars have shown comparable efficacy and safety to branded versions[1-7]

1. Jung YS, et al. *J Gastroenterol Hepatol*. 2015;30:1705-1712. 2. Kang YS, et al. *Dig Dis Sci*. 2015;60:951-956. 3. Park SH, et al. *Expert Rev Gastroenterol Hepatol*. 2015;9(Suppl 1):35-44. 4. Keil R, et al. *Scand J Gastroenterol*. 2016;51(9):1062-1068. 5. Gesce KB, et al. *J Crohns Colitis*. 2016;10:133-140. 6. Farkas K, et al. *J Crohns Colitis*. 2016;10(11):1273-1278. 7. Jahnsen J, et al. *Expert Rev Gastroenterol Hepatol*. 2015;9(Supp 1):45-52.

Switching from Reference Infliximab to CT-P13: NOR-SWITCH

- Phase IV, multi-indication, prospective, non-medical switch study by Norwegian government
- 52-week, randomized, double-blind, non-inferiority study
- 482 patients were randomly assigned IFX vs. CT-P13
- Primary endpoint was “disease worsening”



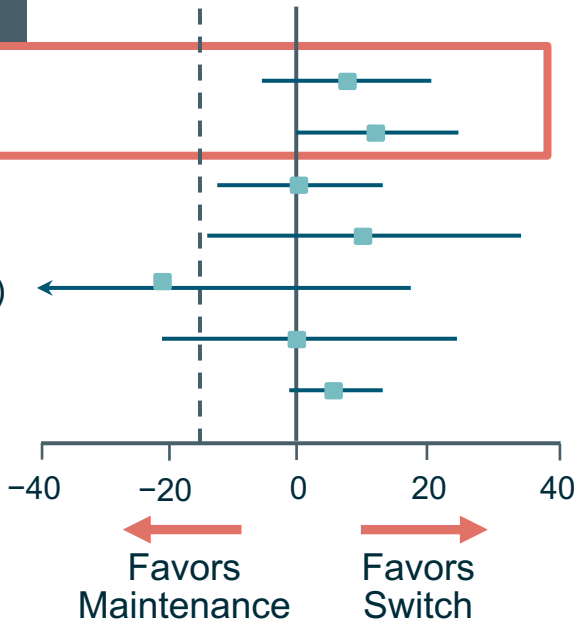
Jorgensen K, et al. *Lancet*. 2017;389(10086):2304-2316.

CME OUTFITTERS

Long-Term Efficacy and Safety of CT-P13: NOR-SWITCH OLE

Diagnosis	Maintenance (n = 190)	Switch (n = 173)	Risk Difference (95% CI)
Crohn's disease	13/63 (20.6%)	8/61 (13.1%)	7.9% (−5.2 to 21)
Ulcerative colitis	6/39 (15.4%)	1/35 (2.9%)	12.4% (−0.1 to 25)
Spondyloarthritis	3/38 (7.9%)	2/28 (7.1%)	0.6% (−12.2 to 13.5)
Rheumatoid arthritis	9/26 (34.6%)	6/27 (22.2%)	10.5% (−13.6 to 34.6)
Psoriatic arthritis	1/8 (12.5%)	3/9 (33.3%)	−20.8% (−59.1 to 17.6)
Psoriasis	0/16 (0%)	0/13 (0%)	0% (−20.6 to 24.7)
Overall	32/190 (16.8%)	20/173 (11.6%)	5.9% (−1.1 to 12.9)

CI prespecified noninferiority margin: -15%



Followed for 78 weeks

CI = confidence interval

Goll GL, et al. *J Int Med*. 2019;285(6):653-669.

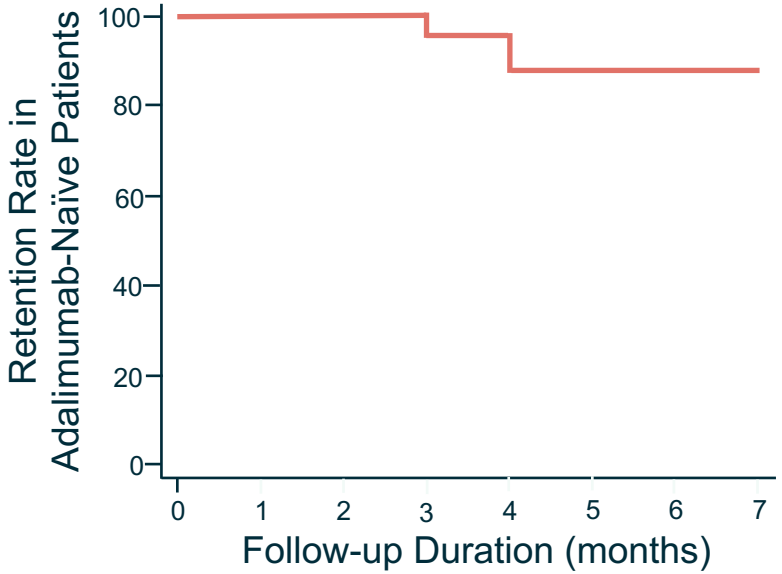
CME OUTFITTERS

Application to Practice: Clinical Scenarios

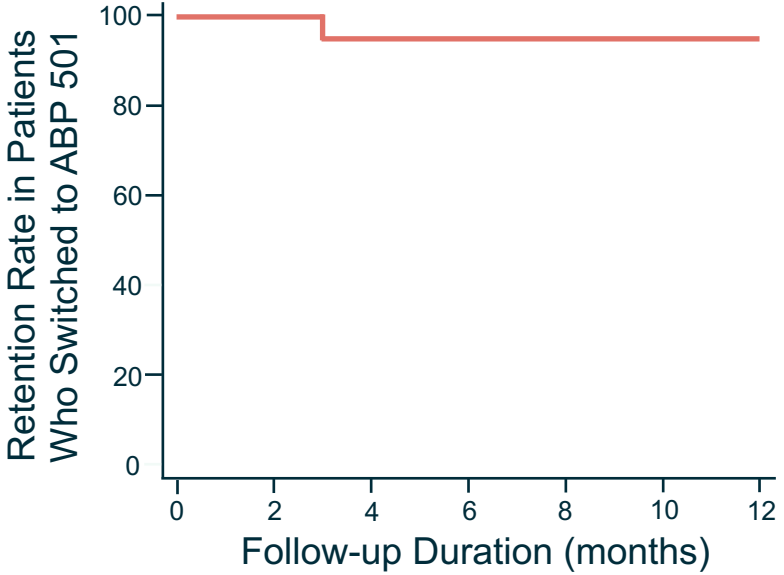
- Your patient, Andrew, was recently switched to an infliximab biosimilar
- **How do you plan to ensure that Andrew's new regimen is working for him?**
- **Is there something you would do differently because your patient is now on a biosimilar?**

Switching from Adalimumab to ABP 501 in CD: Observational Study

Retention Rate in Adalimumab-Naïve Patients



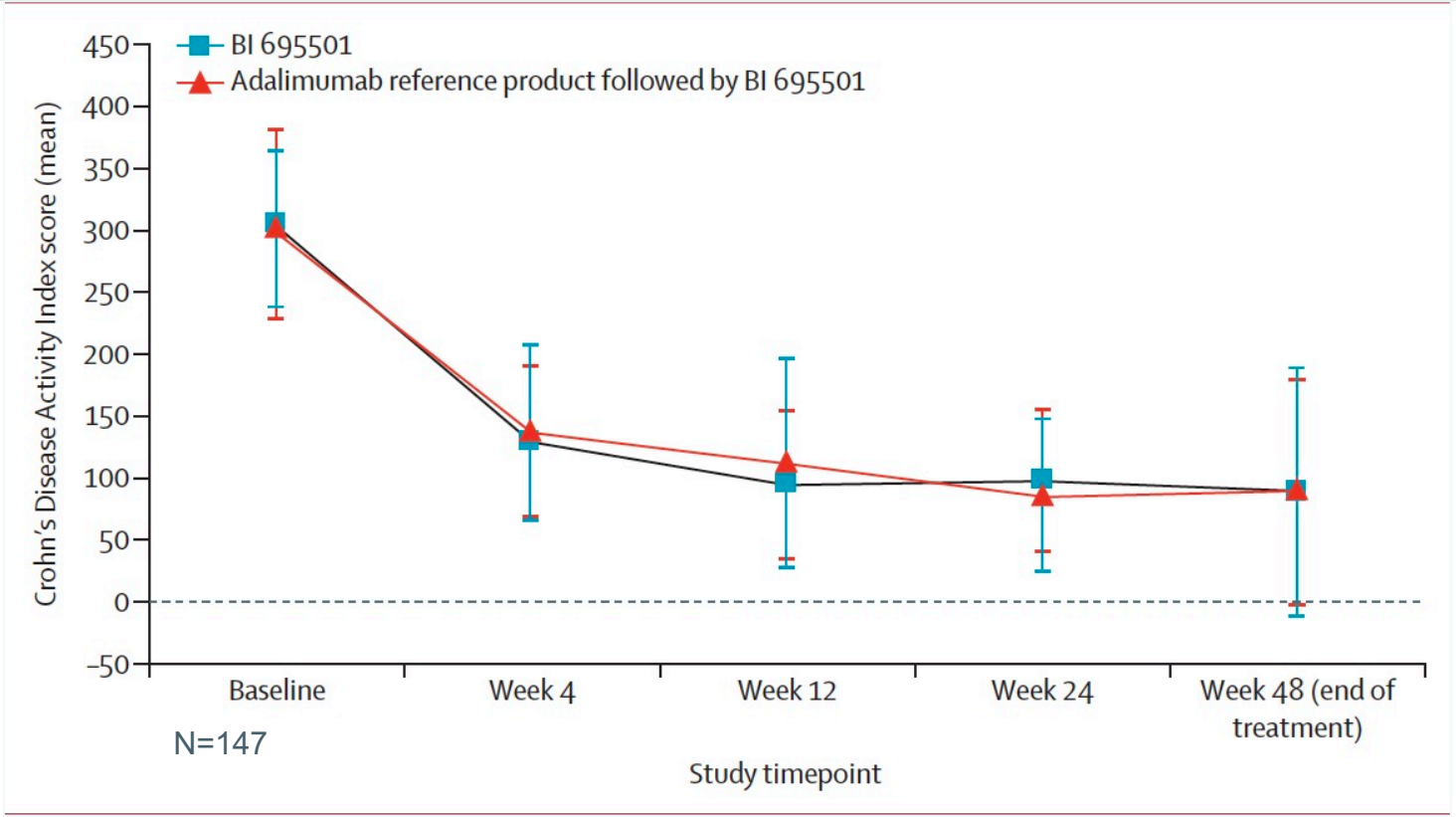
Retention Rate in Patients Switched from Adalimumab Originator



Clinical response (60%) and remission (56%) rates at 3 months were comparable to previously reported rates for adalimumab

Ribaldone DG, et al. *Rev Esp Enferm Dig.* 2020;112(3):195-200.

VOLTAIRE-CD:
DBRCT Comparing ADA to ADA-adbm



DBRCT = double blind randomized controlled trial, ADA = adalimumab, BI695501 = adalimumab-adbm

Hanauer S, et al. *Lancet Gastroenterol Hepatol*. 2021; 6: 816–25

CME OUTFITTERS

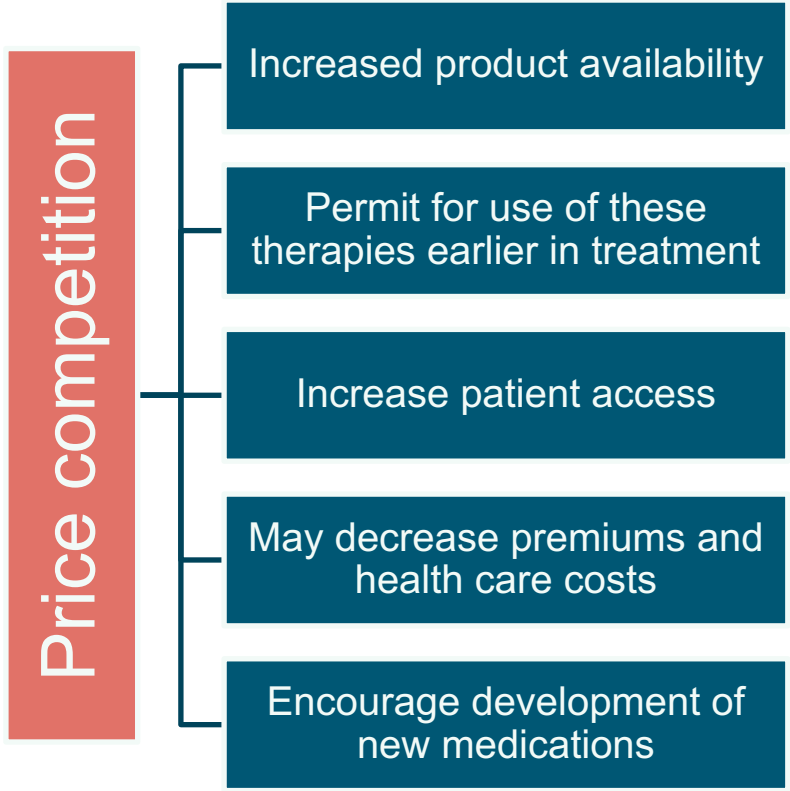
Biosimilars in IBD: The Bottom Line

- Data support similar efficacy in new starts
- Growing evidence to support safety and efficacy of switching for patients in remission
- Accumulating data for “reverse switching, multiple switching, and cross-switching among biosimilars”

Kurti Z, et al. *Exp Opinion on Biological Ther*. 2018;18(6):633-640.

Biosimilars: Additional Benefits

- Reduced expenditure with drug development and FDA approval process
- If adopted, drug costs in the United States could be reduced by **$100 billion** over the next 5 years



Dutta B, et al. *BioDrugs*. 2020;34:159-170.

Application to Practice: Clinical Scenarios

- A health care plan recently made the decision to switch all patients with IBD taking Remicade (infliximab reference) to a biosimilar
- **What would you tell your patients?**

CME OUTFITTERS

Implement team-based strategies to enhance patient-clinician shared decision-making (SDM) regarding the use of biosimilars.

LEARNING OBJECTIVE 3

Audience Response

What is the main source of patient education on biosimilars in your practice?

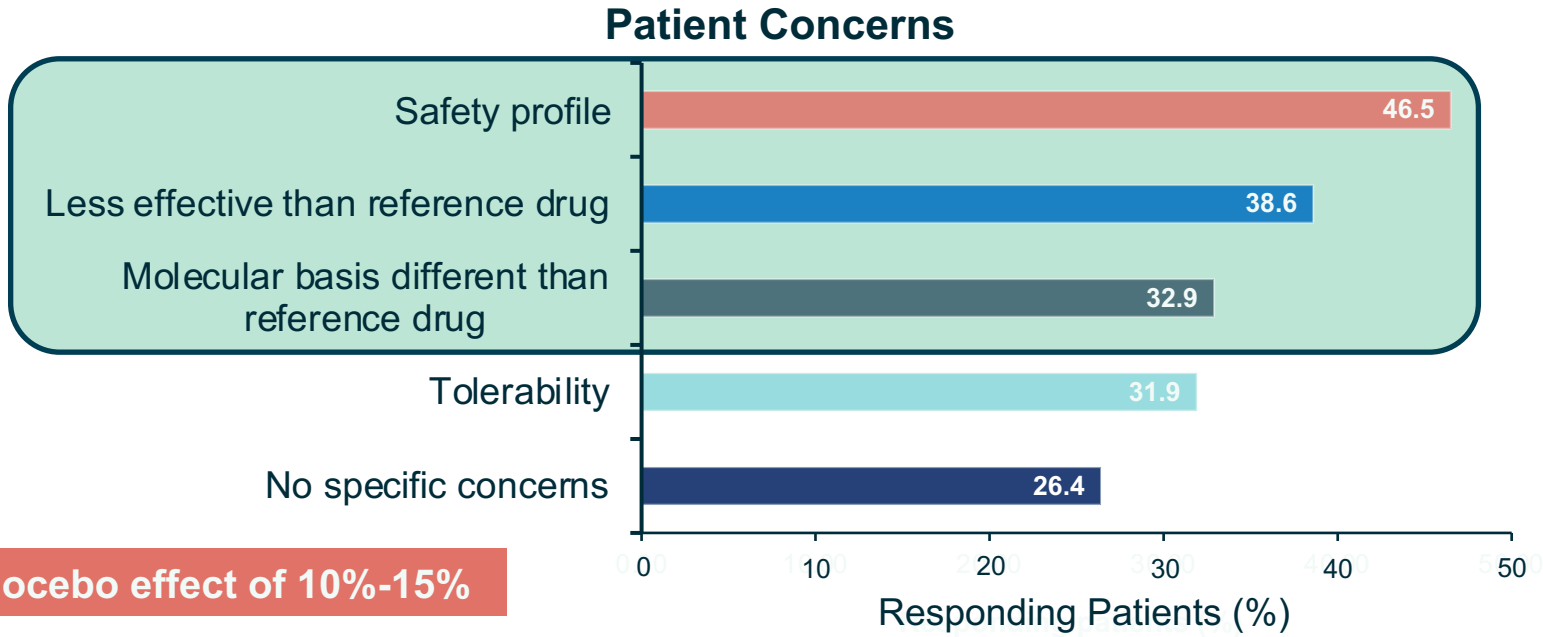
A. Physicians
B. Nurse practitioners, PAs, nurses
C. Patient advocacy groups
D. Pharmaceutical companies
E. None of the above

CME OUTFITTERS


Patient Voice:
Gaps in Patient-Provider
Communication

Patients Are Concerned About Biosimilars

Majority of patients (62%) never heard of biosimilars



A nocebo effect of 10%-15%

Pouillon L, et al. *Expert Rev Clin Immunol*. 2018;14(9):739-749. Peyrin-Biroulet L, et al. *J Crohn's Colitis*. 2017;11:128-133.

As a patient, please tell us how effective health care providers are in informing you about the differences between biosimilars and generic agents in the management of your disease?

The way that it was explained to me was that it was similar to a generic, and I at first took that at face value, and that was really all the information I was given.

Strategies to Minimize the Nocebo Effect

Physician-Patient Communication

- Physician's awareness of the nocebo effect
- Patients' involvement in the decision-making process
- Non-verbal communication

Multidisciplinary Management

- Cooperation between gastroenterologists, nurse practitioners, physician assistants, nurses, and pharmacists to educate patients on biosimilars

Nocebo Effect

Negative effect of a pharmacological or non-pharmacological medical treatment that is induced by patients' expectations and is unrelated to the physiological action of the treatment

Detecting the Nocebo Effect

- Using tools to evaluate patients' expectations and detect subjects at increased risk of nocebo effect (e.g., Perceived Sensitivity to Medicines and Stanford Expectations of Treatment Scale)

Social Observational Learning

- Taking into account individual patients' characteristics to facilitate education and SDM

Modified from D'Amico F, et al. *Expert Opinion on Biological Therapy.* 2021;21(1):47-55.

Utilizing SDM

- Patient and clinician share equally in the decision-making process
- Patient's values, goals, and concerns are considered
- Helps patients learn more about their condition and treatment options

Fox JC, et al. *Mayo Clin Proc Innov Qual Outcomes*. 2020;4(2):183-189.

Patient Education

There is a need for patient education about biosimilars:

- Use of therapy in the specific disease
- Regulatory requirements and safety of biosimilars
- Delivery/administration of the agent
- Insurance coverage
- Advocacy groups

Jacobs I, et al. *Patient Prefer Adherence*. 2016;10:937-948.

Application to Practice: Clinical Scenarios

- Your patient, Sandy, was switched to an infliximab biosimilar a couple months ago
- She wants to get COVID-19 vaccination but is concerned about safety because the medication she is taking is relatively new
- **What will you tell Sandy?**

SMART Goals

Specific, **M**easurable, **A**ttainable, **R**elevant, **T**imely

- Biosimilars are appropriate, safe, and effective for the same indications as the reference product; you should stay abreast of recent clinical trial data
- Do not use a biosimilar if the patient has a prior history of non-response, adverse effects, or antibodies to the reference product
- Recognize which patients in your practice are eligible for a switch to a biosimilar
- Involve patients in the decision-making process to consider switching to a biosimilar

To Ask a Question

Please select the *Ask Question* tab below the slide viewer.

Please include the faculty member's name if the question is specifically for them.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