Comprehensive Update of BIOSIMILAR THERAPIES: Your Questions Answered

This activity is a collaboration of the AGA Institute and the Crohn's & Colitis Foundation.
This program is supported by independent education grants from Boehringer Ingelheim Pharmaceuticals, Inc. and Pfizer Inc.

Polling Questions

How comfortable do you feel discussing biosimilars with your IBD patients?

- Very comfortable
- Somewhat comfortable
- Not at all comfortable

Polling Questions

Biosimilars have the same effectiveness and safety profile as the originator biologic.

- True
- False

Polling Questions

If a new biosimilar therapy demonstrates similar safety and effectiveness to the originator biologic in rheumatoid arthritis, what is your opinion regarding its use in IBD?

- If it works similar to the originator therapy in rheumatoid arthritis, I am satisfied that it will work similarly in IBD.
- Just because it works similar to the originator doesn't mean it will work similar to the originator in IBD, more study is needed
- I don't know

Disclosures – Brian Feagan

Grant/Research Support: AbbVie Inc., Amgen Inc., AstraZeneca/MedImmune Ltd., Atlantic Pharmaceuticals Ltd., Boehringer-Ingelheim, Celgene Corporation, Celltech, Genentech Inc/Hoffmann-La Roche Ltd., Gilead Sciences Inc., GlaxoSmithKline (GSK), Janssen Research & Development LLC., Pfizer Inc., Receptos Inc. / Celgene International, Sanofi, Santarus Inc., Takeda Development Center Americas Inc., Tillotts Pharma AG, UCB

Consultant: Abbott/AbbVie, Ablynx, Akebia Therapeutics, Allergan, Amgen, Applied Molecular Transport Inc., Astra Zeneca, Atlantic Pharma, Avir Pharma, Baxter Healthcare Corp., Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring Pharma, Roche/Genentech, Galapagos, GiCare Pharma, Gilead, Given Imaging Inc., GSK, Inception IBD Inc, Ironwood Pharma, Janssen Biotech (Centocor), JnJ/Janssen, Kyowa Kakko Kirin Co Ltd., Lexicon, Lilly, Lycera BioTech, Merck, Mesoblast Pharma, Millennium, Nektar, Nestles, Nextbiotix, Novonordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Progenity, Protagonist, Receptos, Roche/Genentech, Salix Pharma, Serano, Shire, Sigmoid Pharma, Synergy Pharma Inc., Takeda, Teva Pharma, TiGenix, Tillotts, UCB Pharma, Vertex Pharma, Vivelix Pharma, VHsquared Ltd., Warner-Chilcott, Wyeth, Zealand, Zyngenia

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Janssen Orthobiotech	Consultant, Research, Funding to University of PA (IBD Fellow Education)
Luitpold/American Regent	Consulting, Honorarium (CME Program)
Merck	Honorarium (CME Program)
McMahon Publishing	Author (Honorarium)
Pfizer Pharmaceuticals	Consultant, Funding to University of PA (IBD Fellow Education)
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Takeda	Consultant, Funding to University of PA (IBD Fellow Education)
UCB	Consultant, Research
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Disclosures – David Rubin

Consultant: Abbvie, Abgenomics, Allergan, Inc., Amgen, Celgene Corporation, Forward Pharma, Genentech/Roche, Janssen Pharmaceuticals, Merck & Co., Inc., Miraca Life Sciences, Mitsubishi Tanabe Pharma Development America, Inc., Napo Pharmaceuticals, Pfizer, Salix Pharmaceuticals, Inc., Samsung Bioepis, Sandoz Pharmaceuticals, Shire Takeda, Target PharmaSolutions, Inc.

Grant Support: Abbvie, Genentech/Roche, Janssen Pharmaceuticals, Prometheus Laboratories, Shire, Takeda, UCB Pharma

Board of Trustees: American College of Gastroenterology

Co-Founder, CFO: Cornerstones Health, Inc. (non-profit)

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Biosimilars In IBD

Gary R Lichtenstein, MD
Director, Center for IBD
University of Pennsylvania School of Medicine
Hospital of the University of PA
Philadelphia, PA

Biologic Agents in the U.S.

- Account for 1% of all written prescriptions
- Account for 28% of drug spending

Sarpatwari A., et al. N Engl J Med 2015; 372:2380-2382.

Biosimilar Cost

- Average daily cost for a biologic agent in the USA is US $45, compared with only $2 for a chemical drug[1]
- Global sales of biologic agents are expected to reach $180 billion by 2017 [2]
- ~50% of the sales coming from only 11 biologic agents that face loss of exclusivity by 2022 [3]
- The cumulative savings to health-care systems in the EU and USA, as a result of the use of biosimilars, could exceed US $56 billion, in aggregate over the next 5 years, and might reach as much as $112 billion. [4]

1- Emerton, D. A. BioProcess Int. 11, 6–14 (2013).
2- Visiongain. https://www.visiongain.com/Report/1048/World-Biological-Drugs-Market-2013-2023 (2013).
3- Lawrence, S. Nat. Biotechnol. 32, 626–632 (2014).
4- IMS Health https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Documents/IMS_Institute_Biosimilar_Brief_March_2016.pdf (2016).

What are Biosimilars?

EU Definition*	•A biosimilar is a biological medicinal product that contains a *version of the active substance* of an already authorised original biological medicinal product (reference medicinal product). •A biosimilar demonstrates *similarity* to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise
FDA Definition**	• The biological product is *highly similar* to the reference product notwithstanding minor differences in clinically inactive components; And • There are *no clinically meaningful differences* between the biological product and the reference product in terms of the safety, purity, and potency of the product

* Guideline on Similar Biological Medicinal Products, CHMP/437/04 Rev 1
**Biologics Price Competition and Innovation Act, 42 USC 262(i)(2); see also, 42 USC 262(k)(2)

Biosimilar

- Must have
  - the same strength and
  - dosage form (injectable, for example) and
  - route of administration

  as the reference product

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm436399.htm

Biologics Differ From Small Molecules

	Biologics[1]	Small Molecules[1]
Composition	Protein	Organic chemical
Structure	Variable 3D structure	Well defined structure
Administration	Parenteral	Oral
Degradation	Catabolism	Metabolism
Mechanism of Action (MOA)	Blocking or Depletion	Enzyme Inhibition
Manufacturing Cost	High	Low/Variable

Biologics

- Require more labor to control and regulate the manufacturing process[2]
- Have more expensive quality control and stability testing[2]
- Require extensive record keeping for quality assurance, lengthening time to batch availability[2]

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1. Mocsai A, et al. *BMC Med.* 2014;12:43.
2. Geigert J. *The Challenge of CMC Regulatory Compliance for Biopharmaceuticals and Other Biologics.* 2nd edition. ed. New York: Springer; 2013.

Clarifying Terminology

Biobetter (or Biosuperior):

- A new class of biosimilars, which go beyond mimicking the original biologic product to provide improvements in one or various aspects of their clinical profile, through changes in chemistry, alteration in the formulation and innovative delivery

Interchangeability:

- The medical practice of changing one medicine for another that is expected to have the same clinical result in a given clinical setting and in any patient, on the initiative or with the agreement of the prescriber
  - No US biosimilar agents currently deemed interchangeable

Principle Requirements for the Extrapolation of Indications of Biosimilars

FDA Regulation[1]

Scientific justification for extrapolation should address the following issues for the tested and extrapolated conditions of use:

- **the mechanism(s) of action in each condition of use for which licensure is sought**
- **the pharmacokinetics and biodistribution of the product in different patient populations**
- **the immunogenicity of the product in different patient populations**
- **differences in expected toxicities in each condition of use and patient population**
- **any factor that could affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought**

1- US Department of Health and Human Services, US Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Scientific considerations in demonstrating biosimilarity to a reference product. US Food and Drug Administration http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (2015).

Extrapolation of Clinical Data Across Indications

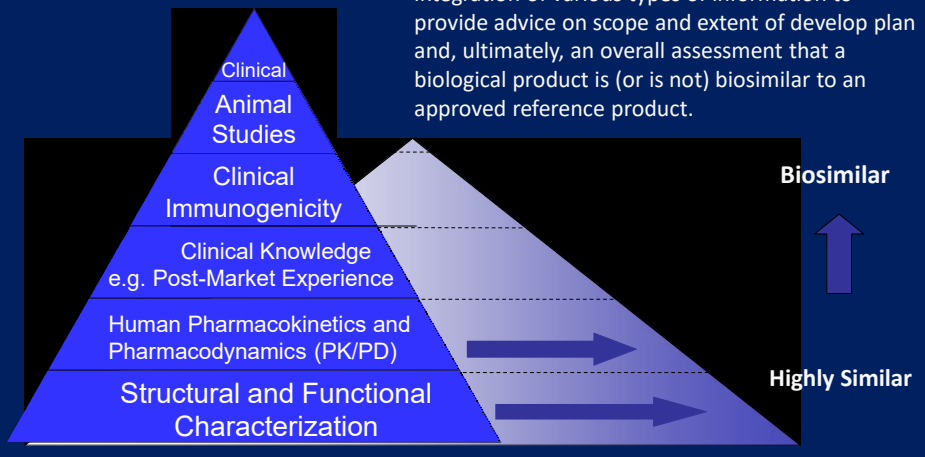
The **majority of indications** for infliximab-dyyb **were extrapolated** based on the biosimilarity exercise by comparing it with Remicade®[3].

1. Yoo D et al. Ann Rheum Dis. 2013;72:1613-1620.
2. Park W et al. Ann Rheum Dis. 2013;72:1605-1612.
3. FDA approves Inflectra, a biosimilar to Remicade [news release]. Silver Spring, MD: US Food and Drug Administration; April 5, 2016. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM494227.htm. Accessed May 7, 2017

Totality of the Evidence

No "one size fits all" assessment :

FDA scientists will evaluate the applicant's integration of various types of information to provide advice on scope and extent of develop plan and, ultimately, an overall assessment that a biological product is (or is not) biosimilar to an approved reference product.



Comparison Across Various Biosimilar Regulations: Extrapolation of Indication

US	EU	Japan	Canada	WHO
Possible with sufficient scientific justification addressing e.g. MoA in each proposed indication, PK and bio distribution in different populations; difference in expected toxicities in each population	Possible depending on clinical experience, literature, MoAof proposed indications, safety issues in sub populations Concept paper proposes revising these criteria	Possible if a similar pharmacological result can be expected in the new indication Not possible if the MoA differs for each indication or is not clear	Possible depending on MoA, pathophysiological mechanisms of disease, safety profile in relevant indications and/or populations, and clinical experience with reference product	Possible if, e.g. sensitive clinical test model was used; MoA and/or receptors are the same (or a strong scientific rational and additional is provided); and no special safety issues are expected in the new indication

Celltrion Conducted Two Large RCTs with CT-P13 (infliximab biosimilar) Based on the EMA Guidelines

A randomised, double-blind, multicentre, pallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study

Won Park, Pawel Hrycaj, Slawomir Jeka, et al.

***Ann Rheum Dis* 2013;72:1605**

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

Dae Hyun Yoo, Pawel Htycaj, Pedro Miranda, et al.

Ann Rheum Dis 2013;72:1613

CT-P13 Clinical Trials Supporting the Therapeutic Indications

Disease	Clinical Trial	Population	N	Primary Endpoint	Dosing Regimen
Rheumatoid Arthritis	PLANETRA (phase III)	Established RA	606	ACR20 at Wk 30	CT-P13 or Remicade (3 mg/kg) at Wks 0, 2, 6 followed by q8w infusions through Wk 54 LTE: Only CT-P13 from Wk 54-102 (Remicade pts switch to CT-P13 at Wk 54)
Ankylosing Spondylitis	PLANETAS (phase I)	Active AS	250	PK equivalence at steady state (AUC Cmax,ss)	CT-P13 or Remicade (5 mg/kg) at Wks 0, 2, 6 followed by q8w infusions through Wk 54 LTE: Only CT-P13 from Wk 54-102 (Remicade pts switch to CT-P13 at Wk 54)

Yoo, et al. *Ann Rheum Dis*. 2013;72:1613-20. Park, et al. *Ann Rheum Dis*. 2013;72:1605-1612. Yoo, et al. ACR 2013. Abstract #L1. Parkm et al. ACR 2013. Abstract #L15. www.clinicaltrials.gov accessed 24FEB15 (http://www.clinicaltrials.gov/ct2/show/NCT02096861?term=CT-P13&rank=1).

Switching vs. Substitution

Transition study

Substitution study (single switch)

Interchangeability study (multiple switches)

NOR-SWITCH Trial

Phase IV multi-indication prospective non-medical switch study in Norway by Norwegian govt.
52 weeks randomized, double-blind non-inferiority study

RESULTS:

Primary outcome: disease worsening at 12 months
Remicade 53/202 (26.2%) vs. CT-P13 61/206 (29.6%)

Anti-drug antibodies:
Remicade 7.1%
CT-P13 7.9%

Disease Worsening

	Remicade	CT-P13
CD (n=155)	14 (21.%)	23 (36.5%)
UC (n=93)	3 (9.1%)	5 (11.9%)

Jorgensen K, et al. Presented at UEGW 2016. Vienna, Austria. Abstract LB 15.

P III randomised, DB, controlled trial to compare biosimilar infliximab (CT-P13) with infliximab in patients with active Crohn's disease

- 220 pts randomised; 58 study centres /16 countries
- At Week 6, CDAI-70 response to CT-P13 similar to IFX (CT-P13, 71.4%; INX, 75.2%; p-value = 0.5613).
- Similar & consistent trends in proportion achieving CDAI-100 response (CT-P13, 61.9%; IFX, 64.4%; p-value=0.7744) and clinical remission 42.9% and 44.6% (p-value = 0.8329) in CT-P13 and INX treatment group
- **Conclusion**
- Efficacy of CT-P13 similar to IFX in terms of CDAI-70, CDAI-100 and clinical remission up to Week 6 in patients with CD. CT-P13 with a similar safety profile to that of IFX up to Week 6.

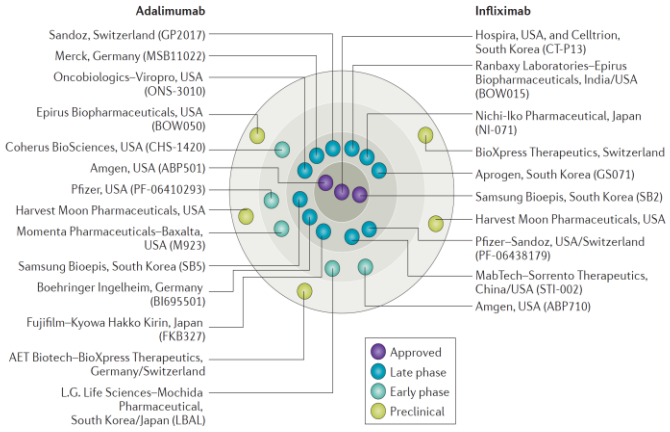
ECCO 2017: Digital Oral Poster 061

The PROSIT cohort of infliximab biosimilar in IBD: a prolonged follow-up on the efficacy and safety of CT-P13 across Italy

- 680 consecutive pts (373 CD, 307 UC) included from academic (n=13) & non-academic (n=12) centers.
- 400 pts naïve to anti-TNFα (192 CD, 208 UC)
- 171 pts (115 CD, 56 UC) had previous exposure to one or more biologics
- 109 pts (66 CD, 43 UC) were switched after mean of 18±10 previous infusions of infliximab (range 3–72)
- A total number of over 4,000 infusions were recorded
- One of largest prospective cohort of patients with IBD treated with CT-P13… **no further signals of difference in safety and clinical efficacy has been observed**.

ECCO 2017 Oral Presentation 005

Biosimilars for Adalimumab and Infliximab in the Pipeline as of 09/2016



Current Biosimilar Nomenclature

- **In** August 2015 FDA proposed a rule for naming biosimilars in. The names include distinguishing suffixes (devoid of meaning), composed of four random lowercase letters.[1]
- **Intention- to avoid inaccurate perception of biosimilars' efficacy[2]**
- **Influences prescribing practice of biosimilars**
- **Current IBD Biosimilar Agents approved:**
  - **Infliximab-hjmt - (Remicade®)- August,1998**
  - **Infliximab-dyyb - (Inflectra®)- April , 2016**
  - **Infliximab-abda - (Renflexis®)- April, 2017**
  - **Adalimumab-atto - (Amjevita®)- September, 2016**
  - **Adalimumab –adbm - (Cyltezo®) – August 2017**

[1] US Food and Drug Administration. https://www.gpo.gov/fdsys/pkg/FR-2015-08-28/html/2015-21382.htm. Accessed May 5, 2017.
[2] Danese S, et al. *Nat Rev Gastroenterol.* 2017;14(1):22-31.

Possible Clinical Scenarios for Biosimilars Use

New Start	• Prescriber choice of reference product or biosimilar
Primary Nonresponder	• Prescriber elects to switch to biosimilar • Prescriber elects to switch to another biologic
Stabilized Responder	• Prescriber elects to maintain original biologic • Prescriber elects to switch to biosimilar (Non-medical SWITCH)
Loss of Response	• If attributed to high titer of ADA, switch to biosimilar is not supported • Prescriber elects to switch to another therapy

Who will Benefit from ~20-30% Cost Savings

- Will this be a cost savings or cost shifting?
  - If total biologic market continues to expand there will be no overall cost-savings on national basis
- If cost/patient falls who will benefit?
  - Third party payers (including government)
  - Not likely individual patients
- Individual patient costs may increase for originator products depending on insurance plan

Biosimilars in IBD
Conclusions

- Biosimilars are not generics
- The FDA allows for extrapolation of indication for biosimilars, and available data suggest that biosimilars to anti-TNFs will behave similarly to their reference products
- Drug assays for reference products are expected to work similarly for biosimilars
- Remember that anti-drug antibodies to reference products WILL cross-react to biosimilars (and vice versa)!
- No biosimilar in the U.S. yet has interchangeable designation, but available European and Asian data suggest that this is likely to be ok, at least in a single transition direction.

Outstanding Questions

- Pathway to biosimilars is still a work-in-progress
- How comfortable will physicians be prescribing biosimilar agents?
- How comfortable will patients be using biosimilar agents?
- How will insurers manage these agents?
- Can we switch from native biologic to biosimilar without immunizing patient ?
- Can we do a double switch without immunizing the patient ie from native biologic to biosimilar and then to another biosimilar ?

Moderated Panel

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