CONTROVERSIES IN IBD: HIGHLIGHTS FROM DDW 2016

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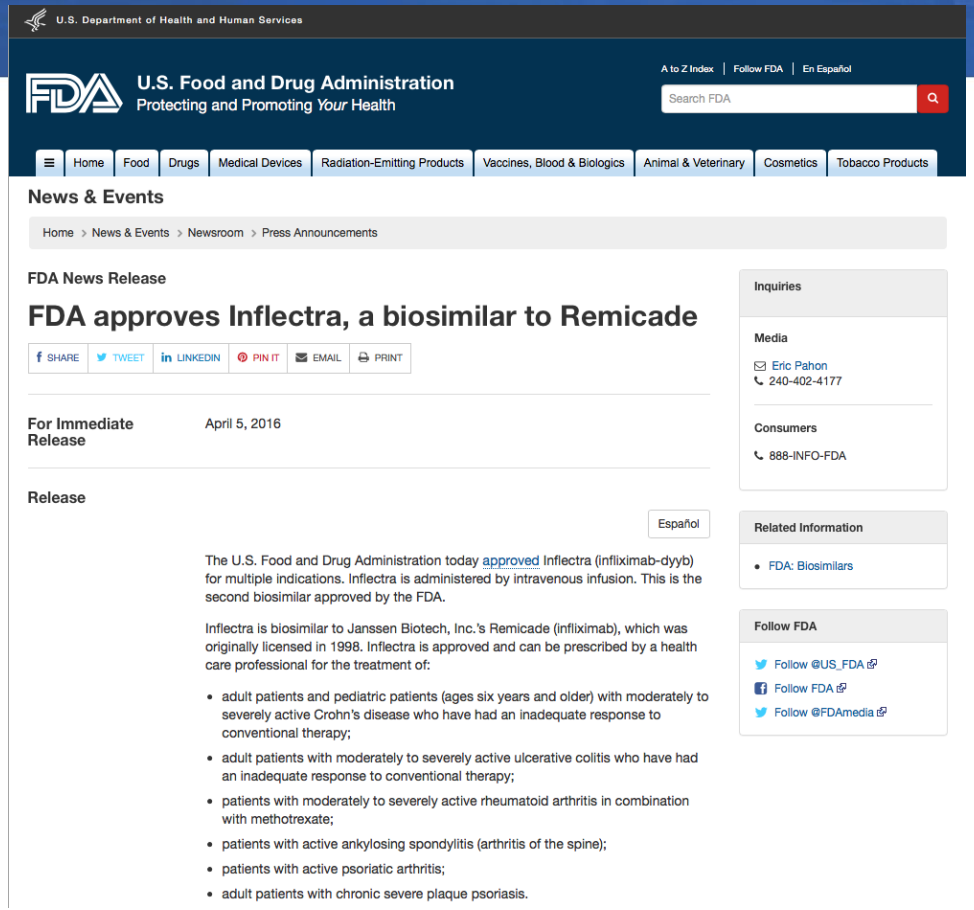
Biosimilars: the latest updates



U.S. Department of Health and Human Services

U.S. Food and Drug Administration
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FDA News Release

FDA approves Inflectra, a biosimilar to Remicade

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For Immediate Release

April 5, 2016

Release

Español

The U.S. Food and Drug Administration today approved Inflectra (infliximab-dyyb) for multiple indications. Inflectra is administered by intravenous infusion. This is the second biosimilar approved by the FDA.

Inflectra is biosimilar to Janssen Biotech, Inc.'s Remicade (infliximab), which was originally licensed in 1998. Inflectra is approved and can be prescribed by a health care professional for the treatment of:

- adult patients and pediatric patients (ages six years and older) with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy;
- adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy;
- patients with moderately to severely active rheumatoid arthritis in combination with methotrexate;
- patients with active ankylosing spondylitis (arthritis of the spine);
- patients with active psoriatic arthritis;
- adult patients with chronic severe plaque psoriasis.

Inquiries

Media

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Consumers

888-INFO-FDA

Related Information

- FDA: Biosimilars

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Approved by European Medical Association in 2013

US Approval for:

- **Adult and pediatric (ages 6+ yrs) moderate to severe Crohn's disease**
- **Adult moderate to severe UC**
- Moderate to severely active RA in combination with MTX
- Active ankylosing spondylitis
- Active psoriatic arthritis
- Chronic severe plaque psoriasis

Biosimilars: FDA definitions and requirements

- A biological product that is ***HIGHLY similar*** to the reference product notwithstanding **minor** differences in ***clinically inactive*** components
- No clinically meaningful difference between the biological product and the reference product in terms of:
  - **Safety**
  - **Purity**
  - **Potency**

FDA US Biologics Price Competition and Innovation Act of 2009

Biosimilars: FDA definitions and requirements

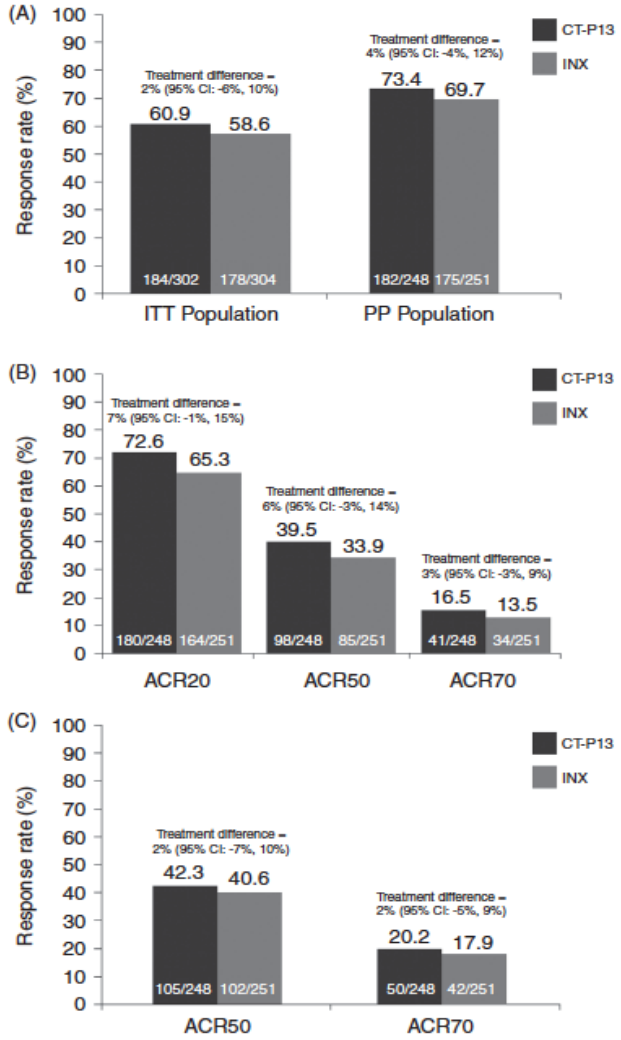
- Clinical trials not required, but at least one comparative study
- Indication extrapolation is possible
- Interchangeability – possible, if biosimilar can be ***alternated*** with the reference product without loss of efficacy or change in the risk of AEs
  - Substitutions may occur at the pharmacy level

FDA US Biologics Price Competition and Innovation Act of 2009

CT-P13 (biosimilar to infliximab): PLANETRA findings

PLANETRA (RA) – IFX or CT-P13 3mg/kg induction and q 8 wk maintenance + MTX (12.5-25mg/wk)

- Equivalent efficacy of CT-P13 & IFX at week 30
- No differences in AEs, comparable pharmacokinetics and immunogenicity

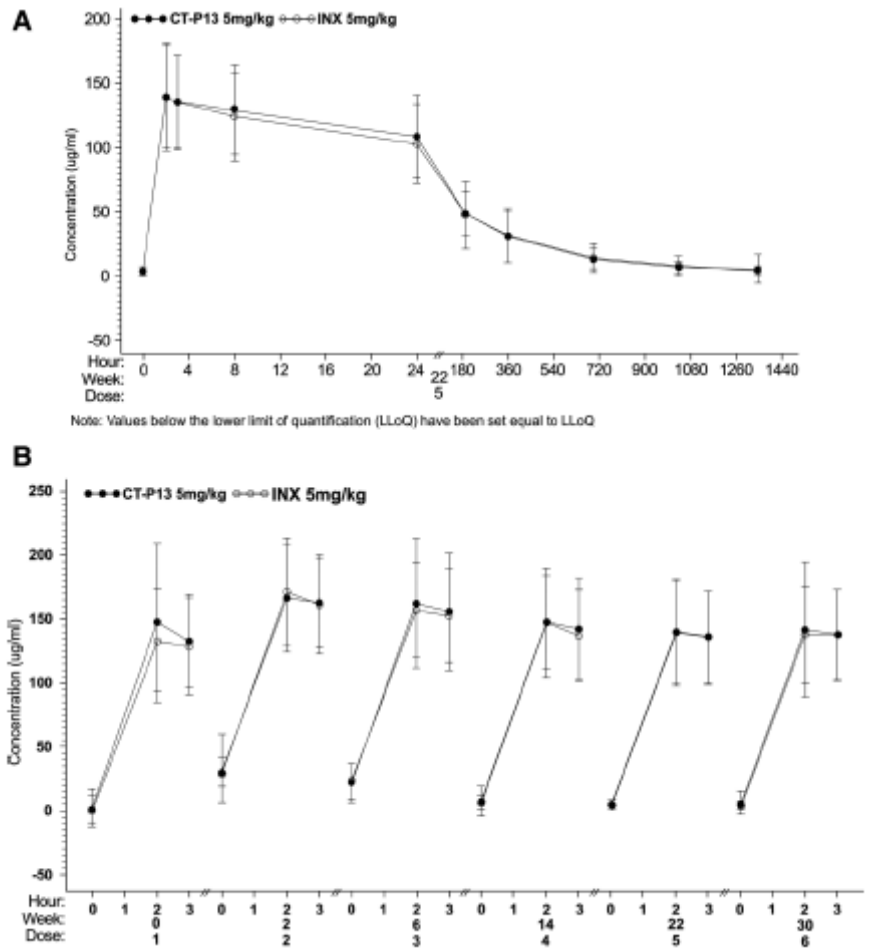


Yoo et al. Ann Rheum Dis. 2013;72:1613-1620

CT-P13 (biosimilar to infliximab): PLANETAS findings

PLANETAS (AS) – IFX or CT-P13 5 mg/kg induction and q 8 wk maintenance until week 30

- Equivalent steady state PK of CT-P13 & IFX
- Similar efficacy btwn both groups
- No differences in AEs, immunogenicity



Park et al. Ann Rheum Dis. 2013;72:1605-1612.

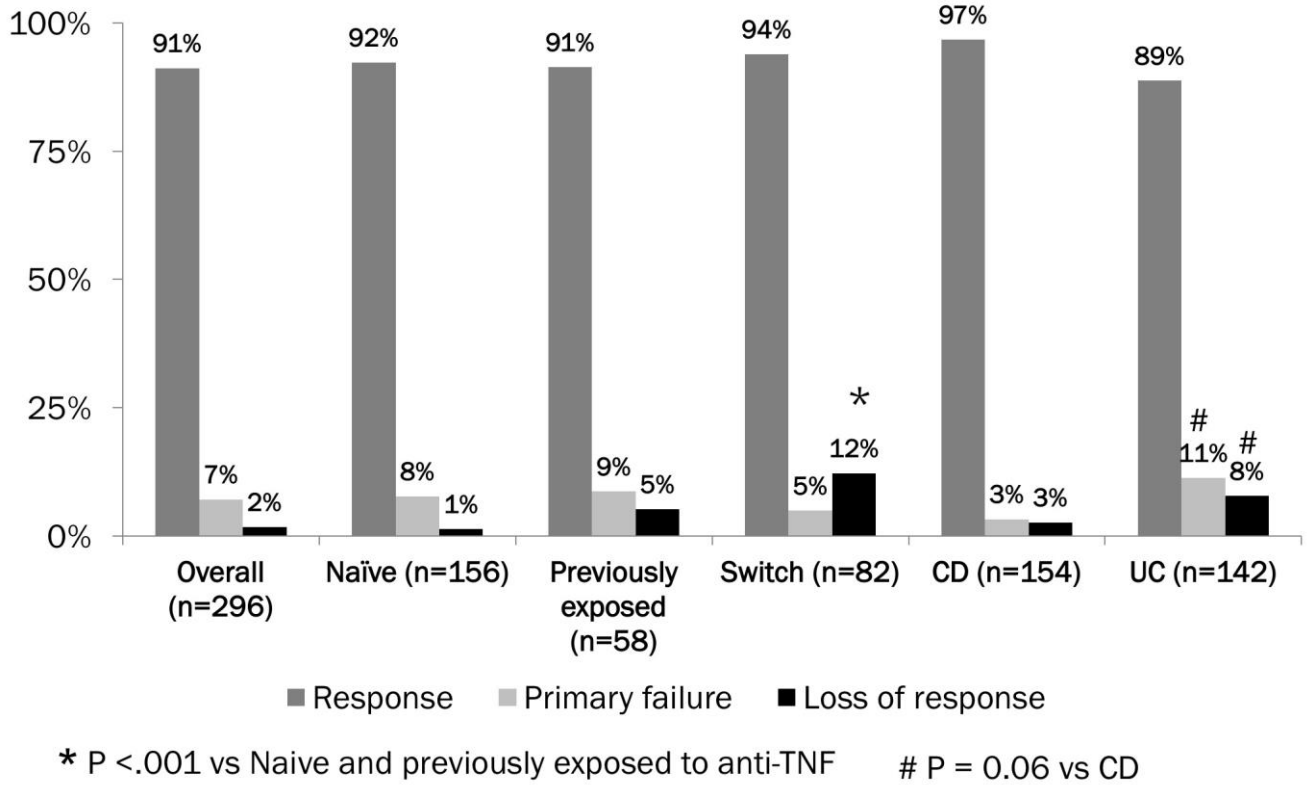
The PROSIT-BIO Cohort of the IG-IBD: A Prospective Observational Study of Patients With Inflammatory Bowel Disease Treated With Infliximab Biosimilars

- Study design: prospective, multi-center, observational cohort of 397 (174 UC, 223 CD) patients treated with CT-P13
  - 217/397 (54.7%) naïve to anti-TNF
  - 87/397 (21.9%) previously biologic exposed
  - 93/397 (23.4%) switched to CT-P13 from infliximab
- Adverse events: 8.3%
  - 4.8% stopped biosimilar
  - 5.3% infusion reactions

Fiorino et al. DDW 2016

The PROSIT-BIO Cohort of the IG-IBD: A Prospective Observational Study of Patients With Inflammatory Bowel Disease Treated With Infliximab BioSimilars

- Efficacy assessed after induction regimen or after 2 infusions post-switch
- Response based on HBI and partial Mayo scores



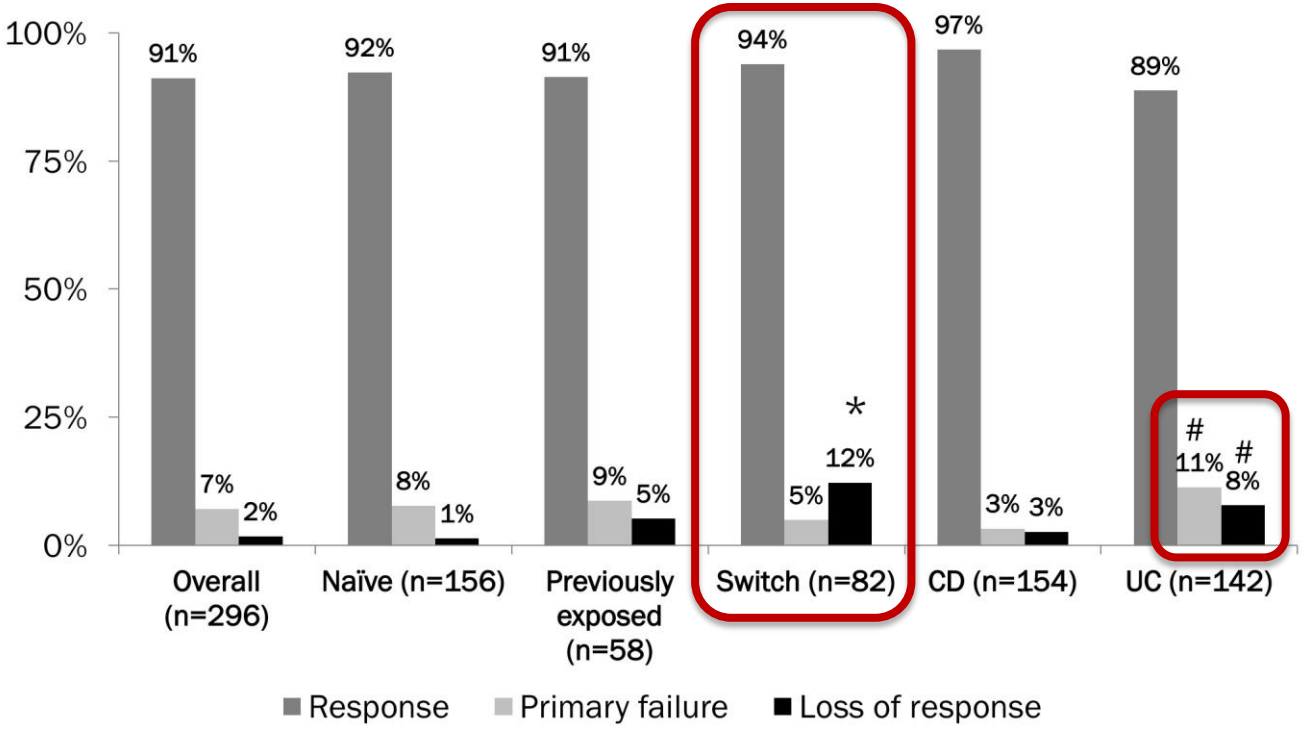
* P <.001 vs Naive and previously exposed to anti-TNF

P = 0.06 vs CD

Fiorino et al. DDW 2016

The PROSIT-BIO Cohort of the IG-IBD: A Prospective Observational Study of Patients With Inflammatory Bowel Disease Treated With Infliximab BioSimilars

- ***5-fold*** **increased loss of response following a switch from IFX to CT-P13**
- Possible trend towards increased primary nonresponse or loss of response in UC patients



Fiorino et al. DDW 2016

Biosimilar Infliximab Is Effective and Safe in Inflammatory Bowel Disease Patients Naïve to Anti-TNF Therapy: A Tertiary Center Experience from Czech Republic

- **Study population:** 104 ***BIOLOGIC-NAÏVE*** patients (79 CD, 25 UC - 27% with prior surgery, 29% with perianal disease; disease duration, 6.2y; 38% with EIMs) treated with biosimilar infliximab (CT-P13) starting from January 2015

Week 22	Crohn's Disease (n=79)	Ulcerative Colitis (n=25)
Complete/Partial response	**89.6%**	**78.3%**
Mucosal healing (Mayo 0 or 1)	**-**	**50%**
Treatment intensification	**8.7%**	**42.3%**

- Mean trough at week 22: 6.3±9.7µg/ml; 10% developed antibodies
- CT-P13 discontinuation – 8.7%; AEs: 19.2% (10 derm, 10 infxn)
- Conclusion: Real-world *effectiveness* of *biosimilar infliximab* in *biologic-naïve* patients with IBD, is **comparable** to historical rates with originator infliximab

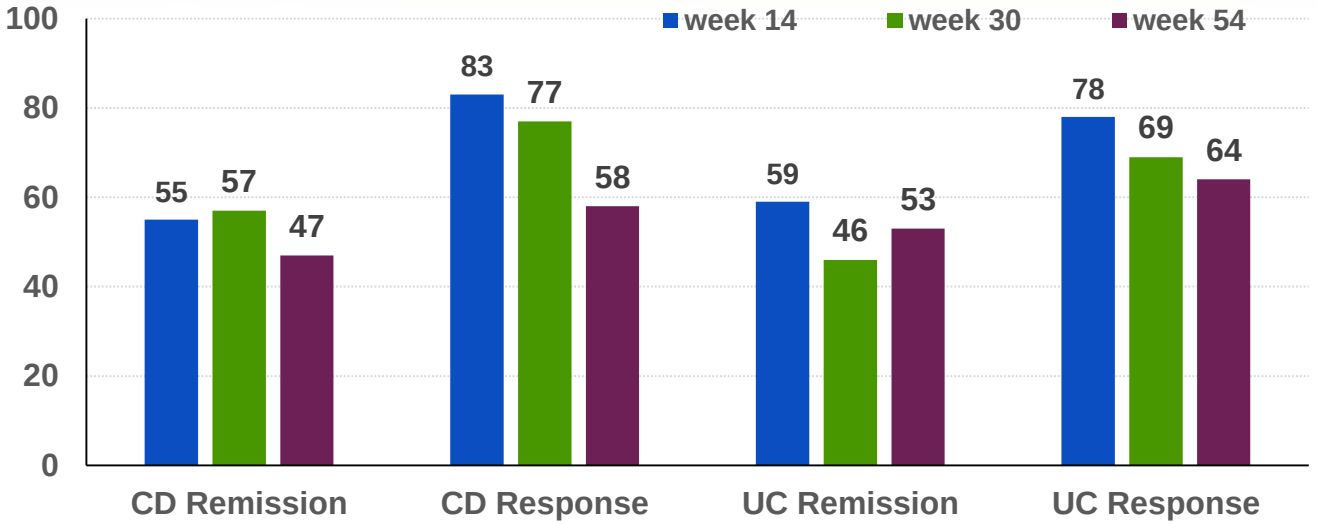
Bortlik MT, et al. DDW 2016, Mo515

Efficacy and Safety of Biosimilar Infliximab After One-Year: Results From a Prospective Nationwide Cohort

- Study design: Prospective, multicenter, observational study
  - No patient had received infliximab within 12 months prior to CT-P13
- Aim: To examine the efficacy and safety of CT-P13 infliximab biosimilar for **induction** and **maintenance** of CD and UC
- Population: 291 IBD patients (184 CD, 107 UC)
  - **25% CD and 14% of UC had prior TNF exposure**
  - 60% CD, 52% UC on concomitant immunosuppressants
- Outcomes of interest: Clinical remission, response, biochemical response at weeks 14, 30, 54

Gecse et al. DDW 2016. Sa1936

Efficacy and Safety of Biosimilar Infliximab After One-Year: Results From a Prospective Nationwide Cohort



- **Previous TNF exposure associated with lower response & remission**
- 21 (6.6%) patients had infusion reactions, 23 (7.9%) had infections, 1 death occurred
- **Conclusion**: CT-P13 biosimilar of infliximab is effective and safe in maintaining remission in UC and CD (no comparison group in this study)

Gecse et al. DDW 2016. Sa1936

Switching of Patients With Inflammatory Bowel Disease From Original Infliximab (Remicade®) to Biosimilar Infliximab (Remsima™) Is Effective and Safe

- Study design: Retrospective observational cohort
- Aim: To evaluate efficacy and safety of switching from original to biosimilar infliximab in CD and UC
- Population: 74 IBD patients (56 CD, 18 UC) on infliximab therapy that were switched to biosimilar (Remsima – CT-P13)
  - Mean time of 3 ± 2.2 yrs of orignator IFX
  - 46% on concomitant azathioprine
  - 69% clinical remission, 22% mild-mod active dz; 5% severe dz
- Outcomes of interest: Disease activity and adverse events

Kolar et al. DDW 2016. Sa1957

Switching of Patients With Inflammatory Bowel Disease From Original Infliximab (Remicade®) to Biosimilar Infliximab (Remsima™) Is Effective and Safe

- Results: Comparing week 0 to week 24 after starting the biosimilar, **no differences** in **CRP, calprotectin, infliximab levels or antibodies**
  - Remission at week 0 - 72%, week 24 – 78%
  - 3 patients stopped IFX due to LOR (1), adverse event (1), LGD (1)
  - No infusion reactions were observed
- Conclusion: Switching to biosimilar IFX appears to be effective and safe
- Limitations: No control IFX brand group for comparison; no long term data on efficacy.

Kolar et al. DDW 2016. Sa1957

Biosimilars for IBD:

- Does the currently available evidence support its interchangeable use in clinical practice?
- How do you counsel your patients re: biosimilars?
- What are the future directions regarding biosimilars for IBD?

Therapeutic drug monitoring: when to check and why? What is already known from the evidence…

- Higher serum IFX concentration is associated with better Crohn's disease remission rates, endoscopy scores and mucosal healing
- Greater proportion of patients with higher serum IFX concentrations achieved clinical remission (ACT 1 & 2)
- Detectable serum trough IFX levels associated with higher UC remission rates and endoscopic improvement
- Antibody formation: decreased response/remission rates, increased drug clearance, increased infusion reactions

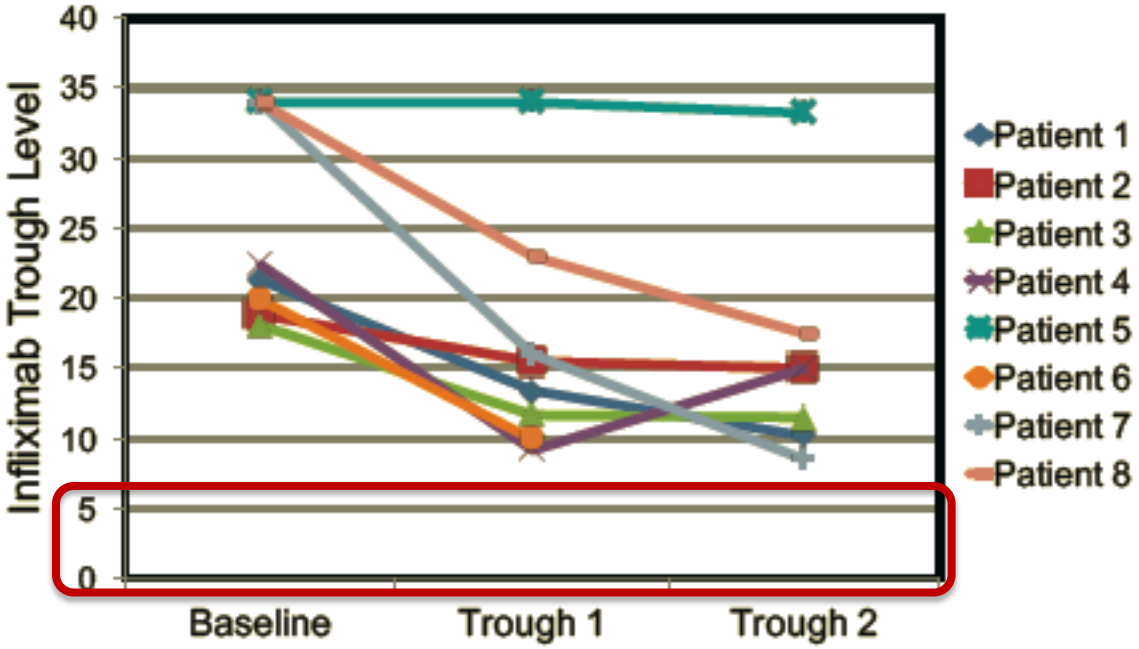
Maser et al. Clin Gastroenterol Hepatol. 2006; 4:1248-54
Seow et al. Gut. 2010; 59:49-54
Reinisch et al. Gastroenterology. 2012.
Van Moerkercke et al. Gastroenterology. 2010.

Rational Infliximab De-escalation in CD using Infliximab Levels

- **Study Population:** 10 CD patients treated with infliximab for at least one year and in ***clinical remission*** for at least 6 months with IFX trough > 10
- **Aim:** Determine whether sustained remission is maintained after dose de-escalation by based on monitoring drug and antibody levels
- **Intervention:** Infliximab levels and antibodies were measured at baseline
  - If infliximab trough > 10 with undetectable ATIs, then the IFX maintenance dose was de-escalated
  - From **10mg/kg or 7.5mg/kg down to 5mg/kg** or from **5mg/kg down to 3mg/kg**
  - Intervals were ***not*** adjusted
  - Patients were followed for 3 infusions post de-escalation
  - HBI scores and infliximab troughs measured at subsequent infusions

Allegretti *et al*. DDW 2016. Sa1974

Rational Infliximab De-escalation in CD using Infliximab Levels



Is this a reasonable strategy to consider for our stable IBD patients on anti-TNFs?

- ***No patient was on combination therapy***
- Mean baseline trough 25.8 (range 18-34) prior to de-escalation
- All trough remained therapeutic (>5) after 2 infusions (but notably lower than baseline)
- ATIs developed in 1 patient
- HBI was 0 during follow-up (30 weeks)

Allegretti *et al*. DDW 2016. Sa1974

Drug Level-Based Dosing Versus Symptom-Based Dose Adaptation in Patients with Crohn's Disease (TAILORIX)

- **Study rationale:** Superior outcomes have been associated with IFX concentrations with a "therapeutic window"
  - Hypothesis: Prospective therapeutic drug monitoring would yield better remission rates compared to symptom based adjustments
- **Study design:** Randomized, double-blind, multi-center, controlled trial of ***biologic naïve*** 167 active (CDAI > 220, CRP >5 and/or fecal calprotectin >250, and endoscopic ulcers present) CD patients
- **Primary endpoint:** Steroid free remission from week 22 to 54 and mucosal healing at 1 year
- **Treatment:** IFX 5mg/kg induction + AZA 2-2.5mg/kg/day

D'Haens *et al*. DDW 2016. Abstract 692

Drug Level-Based Dosing Versus Symptom-Based Dose Adaptation in Patients with Crohn's Disease (TAILORIX)

Week 14 randomization (target for IFX trough > 3 pg/ml):

Group 1: Dose intensification of IFX at **2.5mg/kg increments** based on:

- Clinical symptoms
- Biomarker analysis
- Serum IFX concentrations

Group 2: Dose intensification of IFX from **5mg/kg to 10mg/kg** based on:

- Clinical symptoms
- Biomarker analysis
- Serum IFX concentrations

Group 3: Dose intensification of IFX from **5mg/kg to 10mg/kg** based on:

- Clinical symptoms alone

D'Haens *et al*. DDW 2016. Abstract 692

Drug Level-Based Dosing Versus Symptom-Based Dose Adaptation in Patients with Crohn's Disease (TAILORIX)

	Group 1 (TDM w/IFX increase @ 2.5mg/kg)	Group 2 (TDM w/IFX increase from 5-10mg/kg)	Group 3 (clinical adaptation)
Steroid-free remission	47%	38%	40%
Endoscopic remission (CDEIS < 3) at week 54	49%	51%	45%
Dose intensification	51%	65%	40%

Conclusion: proactive TDM was *NOT* superior to symptom-based dose adaptation

D'Haens *et al*. DDW 2016. Abstract 692

Drug Level-Based Dosing Versus Symptom-Based Dose Adaptation in Patients with Crohn's Disease (TAILORIX)

	Group 1 (TDM w/IFX increase @ 2.5mg/kg)	Group 2 (TDM w/IFX increase from 5-10mg/kg)	Group 3 (clinical adaptation)
< 3) at week 54			
Dose intensification	51%	65%	40%

How should we interpret these findings in our clinical practice?
When should we be assessing anti-TNF trough levels and antibodies?

Conclusion: proactive TDM was *NOT* superior to symptom-based dose adaptation

D'Haens *et al*. DDW 2016. Abstract 692

IBD therapy: is it forever or for the time being?

Reasons to stop IBD therapy

- Costs associated with biologic therapy
- Long term efficacy of combination therapy is unknown
- Long term safety of combination therapy unknown
- Lifestyle/Travel related concerns
- Risks associated with longstanding immunosuppression – infection, malignancy, TNF-associated complications (lupus, psoriasis, neuropathy)

Long-Term Outcome After Infliximab Withdrawal for Sustained Remission in Crohn's Disease

- Study design: Retrospective review of STORI data → infliximab treatment discontinued among patients in sustained steroid-free remission on combination therapy
  - STORI short term results: 45% relapsed after 16 mos, 88% successful IFX rescue
- Aim: To describe the long-term outcomes, composite failures and predictor factors of patients discontinuing IFX
- Subjects: 102 Crohn's patients in CS-free remission ≥ 6 mos on dual therapy (IFX + AZA) for ≥ 1 yr who stopped IFX
- Outcomes of interest: Severe failure (surgery, new perianal lesions), moderate failure (failure of IFX after resumption)

Reenaers et al. DDW 2016. 313

Long-Term Outcome After Infliximab Withdrawal for Sustained Remission in Crohn's Disease

Key findings:

- 21.6% pts did not restart biologic therapy after 78 mo follow up
- 7.8% pts had severe failure (surgery or severe perianal disease) after 45 mo follow-up
- ***70.6% restarted biologic (64 IFX, 8 ADA): median drug holiday of 13 mo***
  - **68.8% successful IFX restarts @ 70 months**
  - 28.2% infliximab non-responders after restart
  - 15.6% developed new perianal disease or required surgery
- Factors associated with severe failure: ***upper GI involvement, WBC > 6K, hgb ≤ 12.5 g/dL***
- ***Median 8 years of follow-up: 15% did not experience any CD failure***

Reenaers et al. DDW 2016. 313

Long-Term Outcome After Infliximab Withdrawal for Sustained Remission in Crohn's Disease

Key findings:

- 21.6% pts did not restart biologic therapy after 78 mo follow up
- 7.8% pts had severe failure (surgery or severe perianal disease) after 45 mo

When can we (or is it too risky) consider anti-TNF discontinuation for our stable Crohn's disease patients?
Do you think these findings are similarly applicable for UC?

- Factors associated with severe failure: ***upper GI involvement, WBC > 6K, hgb ≤ 12.5 g/dL***
- ***Median 8 years of follow-up: 15% did not experience any CD failure***

Reenaers et al. DDW 2016. 313

Azathioprine Dose Reduction in Inflammatory Bowel Disease Patients on Combination Therapy: A Prospective Study

- **Objective:** Investigate if azathioprine dosing can be reduced to improve the risk/benefit profile of combination therapy without compromising on efficacy
- **Study Population:** 81 IBD patients in deep remission > 6 months and on IFX + AZA > 1 year
  - Clinical and endoscopic remission and/or normalization of biomarkers
  - All patients had IFX trough > 2 pg/ml and stable dosing of AZA and IFX
  - **Group A: AZA & IFX dosing unchanged**
  - **Group B: AZA dosing halved, minimum dose 50mg/d**
  - **Group C: AZA discontinued**
- **Primary endpoint:** Clinical relapse (CDAI > 220 with fecal calprotectin > 450 µg/g stools) and/or need to change therapy because of adverse events

Del Tedesco *et al*. DDW 2016. 693

Azathioprine Dose Reduction in Inflammatory Bowel Disease Patients on Combination Therapy: A Prospective Study

	Group A (No change)	Group B (AZA decreased)	Group C (AZA stopped)
Relapse rates	17.8%	11.5%	30.7% *
Mean IFX trough levels	Start: 3.65 pg/ml End: 3.45 pg/ml	Start: 3.95 pg/ml End: 3.6 pg/ml	Start: 4.2 pg/ml End: 2.1 pg/ml *
Antibody formation or decreased IFX trough	14.2%	18.5%	53.8% *

6TGN < 105 pmol was associated with lower IFX levels/ATI formation

Del Tedesco *et al*. DDW 2016. 693

Azathioprine Dose Reduction in Inflammatory Bowel Disease Patients on Combination Therapy: A Prospective Study

	Group A (No change)	Group B (AZA decreased)	Group C (AZA stopped)
Relapse rates	17.8%	11.5%	30.7% *
trough			

Based on these findings, may we safely decrease thiopurine dosing for IBD patients in deep remission on combination therapy?
Does lower thiopurine dosing translate to lower adverse event potential – specifically with malignancy?

6TGN < 105 pmol was associated with lower IFX levels/ATI formation

Del Tedesco *et al*. DDW 2016. 693

CONTROVERSIES IN IBD: HIGHLIGHTS FROM DDW 2016
Take-home points

- Biosimilars are now FDA approved for adult Crohn's disease ulcerative colitis
  - Probable similar efficacy and safety among biologic naïve patients
  - Possible decreased efficacy with IFX to biosimilar switching and for anti-TNF (including IFX) exposed patients
- Longer-term data from the STORI trial suggests high rate of relapse following IFX discontinuation even for patients with stable remission
  - Majority of patients can be safely and effectively re-treated with anti-TNF therapy
- Pro-active therapeutic drug monitoring may not be necessary
- There ***may*** be a subset of patients in stable remission who would benefit from dose de-escalation of anti-TNF or thiopurine dosing