Selecting the Right First-line Biologic Agent

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Personalized Medicine

- **The right drug**
- **The right dose**
- **For the right patient**
- **At the right time**
- **Using the right route**

Ladak SS et al Pain Management Nurs 2007; 8: 140-5

The Right Treatment

- **Pretreatment Genomic Analysis**
  - **Hepatitis C**
  - **Cancer**
  - **TPMT**

Gene Expression Profiles Crohn's Disease

- **37 pt with active CD**
  - **19 colitis**
  - **18 ileitis**
- **Top-five gene set**
  - **TNFAIP6**
  - **S100A8**
  - **IL11**
  - **G0S2**
  - **S100A9**
- **Expression profiles prior to and after anti-TNF treatment**

Crohn's Disease	Predictive Signature for Anti-TNF Response
Ileitis	-
Colitis	100%

Arijs I *et al* Inflam Bowel Dis 2010; 16; 2090-8

IBD: Response to Treatment Microbiome

Biologic /Trial	Bacteria	Relapse Risk
Infliximab STORI Prospective CD Discontinuation Relapse predictors	↓Faecalibacterium prausnitzii ↓Bacteroides	p=0.014 P=0.030 Independent of CrP p=0.0001
Vedolizumab CD and UC Porspective	CD: ↑ butyrate producers UC: Different bacterial metabolites in responders	Lower risk No significant differences

Rajca S *et al*. Inflam Bowel Dis 2014; 20; 978-986
Ananthakrishnan AN *et al*. Cell Host Microbe 2017;21: 603-10

The Right Biologic

- **Infliximab**
- **Adalimumab**
- **Certolizumab pegol**
- **Vedolizumab**
- **Ustekinumab**
- **JAK inhibitors**

Remision at 52 week Biologics

Crohn's Disease	
Anti-TNF 1° Response 60% x 20% yearly loss of response	48%
Ustekinumab	28%
Vedolizumab	25%

Ulcerative Colitis	
Anti-TNF	49%
Tofacitinib	40.6%
Vedolizumab	39%

The Right Patient Circumstances

- **Primary Non-responder to Anti-TNF**
- **Pregnancy**
- **Lymphoma**
- **Demyelinating disease**
- **Cardiac failure**

Factors Predictive of a Primary Non-Response to Anti-TNF: Crohn's

- **Disease duration > 2 years**
- **Small bowel disease**
- **Smoking**
- **Normal CrP**
- **Gene mutations**
  - **FAS-L (fatty acid synthase ligand)**
  - **Caspase 9**

1° Non-Response to an Anti-TNF and Inferior Response to Next Agent

- **Systematic Search**
- **Through May 2017**
- **8 RCTs with biologics**
  - **Stratified for prior exposure to anti-TNF or not**
- **Estimated relative risks of clinical remission**

Remission with 2nd Line Biologic

Primary non-responders	Δ
PNR vs Intolerance	-24%
PNR vs 2° loss of response	-27%

Singh S *et al* J Crohn's & Colitis January 2018

Vedolizumab 1st Line for UC Markov Modeling

- **Univ. of PENN**
- **Hypothetical**
- **35 y/o man with steroid dependent moderate to severe UC**
- **4 models**
  - **1. Vedo prior to IFX plus azathioprine**
  - **4. Vedo after IFX plus azathioprine**

Calculations for 100,000 pt

Outcome at 1 year

	#1 versus #4
Remissions	+ 8981
Lymphoma	- 18
Serious Infections	-1087

Scott FI *et al* Inflam Bowel Diseases Feb 2018; 24: 286-95

The Right Patient Circumstances

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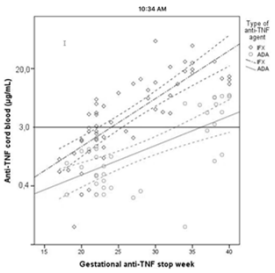
The Right Biologic Pregnancy

- Infliximab
- Adalimumab
- Certolizumab pegol
- Vedolizumab
- Ustekinumab

Optimal Anti-TNF Stop Week During Pregnancy Depends on Anti-TNF Type

- Prospective
- Single center
- 320 live births
  - 131 Anti-TNF
    - 73 Infliximab
    - 58 Adalimumab
- CD 82%, UC 17%, IBDU 1%
- Anti-TNF stopped at various times before delivery
- Cord blood samples measured for Anti-TNF



Kanis SL et al. Rotterdam DDW 2017 Oral # 332c

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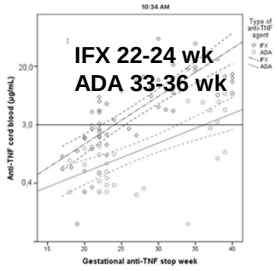

Kanis SL et al. Rotterdam DDW 2017 Oral # 332c

The Right Biologic Pregnancy: Certolizumab

- 16 women with CD
- Certulizumab pegol throughout pregnancy
- Maternal / infant blood levels
  - 14 infants per protocol
- Conclusion: Minimal placental transfer

Certolizumab Blood Levels

	Birth	4 wk	8 wk
Maternal	24.4µg/ml		
Infant	0 in 13 0.042µgml in one	0	0

Mariette X et al Ann Rheum Dis 2018;77:228-33

The Right Biologic Pregnancy

Data from clinical trials and post-marketing reports CD & UC

Vedolizumab Treatment		
Mothers	27	No safety concerns
Fathers	19	

2 Case reports in patients with CD

Ustekinumab Treatment		
Mothers	2	No safety concerns

Mahadevan U *et al* Alim Phar Ther 2017; 45: 941-50
Corrtes X et al J Clin Pharm Ther 2017; 42: 234-6

The Right Patient Circumstances

- Primary Non-responder to Anti-TNF
- Pregnancy
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- Demyelinating disease
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The Right Biologic
Anti-TNF & Lymphoma Risk

- **Micromedex: "increased risk"**

Rheumatoid Arthritis Patients in the UK Number who developed Lymphoma		
Anti-TNF 11, 931	No Anti-TNF 3,367	Hazard Ratio
88	30	1.0

Conclusion: No increased risk

Mercer LK *et al* Ann Rheum Dis 2017;76:497-503

The Right Patient
Special Circumstances

- **Primary Non-responder to Anti-TNF**
- **Pregnancy**
- **Lymphoma**
- **Demyelinating disease**
- **Cardiac failure**

The Right Biologic
Anti-TNF and Demyelinating Disese

- **Micromedex "**New or worsening demyelinating disorders (eg, multiple sclerosis, optic neuritis, peripheral demyelinating disorders including Guillain-Barré syndrome) have rarely been reported"
- Anti-TNF therapy for MS in 2 clinical trials showed worsening
- Many case reports of CNS and peripheral demyelinating disease after anti-TNF therapy
- But, prospective trials and post-marketing registries have not shown a risk

Kemanetzoglou E et al Curr Neurol Neuroscir Rep 2017; 17:36

The Right Patient
Special Circumstances

- **Primary Non-responder to Anti-TNF**
- **Pregnancy**
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The Right Biologic
Anti-TNF & Heart Failure

- **Controversial**
- **Micromedex "**Use should generally be avoided in patients with heart failure; monitor and discontinue if new or worsening symptoms develop"

150pt Heart Failure NYCHA Class III or IV Death or Hospitalization up to 28 wk		
Placebo	IFX 5 mg/kg	IFX 10 mg/kg
5	4	13
		p=0.043

Chung ES *et al* Circulation 2003;107: 3133-40

The Right Biologic

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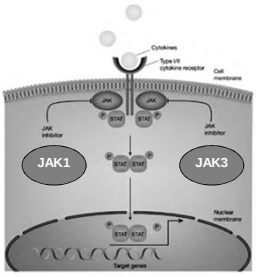
- **JAK inhibitors**

Janus Kinase (JAK) Inhibition

- **JAK phosphorylate activated cytokine receptors**
  - **Recruit STAT transcription**
- **Inhibitors block**
  - **IL-2, IL-4, IL-15, IL-21,**
  - **T_h2 cell differentiation**
  - **IFN-γ, IL-6**
  - **T_h1 cell differentiation**

Signal transducer and activator of transcription



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ORIGINAL ARTICLE

Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis

William J. Sandborn, M.D., Chinyu Su, M.D., Bruce E. Sands, M.D., Geert R. D'Haens, M.D., Séverine Vermeire, M.D., Ph.D., Stefan Schreiber, M.D., Silvio Danese, M.D., Brian G. Feagan, M.D., Walter Reinisch, M.D., Wojciech Niezychowski, M.D., Gary Friedman, M.D., Nervin Lawendy, Pharm.D., Dahong Yu, M.D., Ph.D., Deborah Woodworth, M.B.A., Arnab Mukherjee, Ph.D., Haiying Zhang, Ph.D., Paul Healey, M.D., and Julian Panés, M.D., for the OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators*

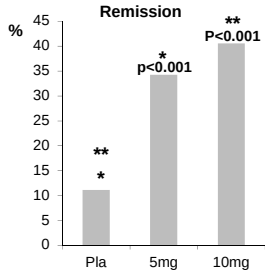
N Engl J Med 2017; 376:1723-1736 | May 4, 2017 | DOI: 10.1056/NEJMoa1606910

CONCLUSIONS

In patients with moderately to severely active ulcerative colitis, tofacitinib was more effective as induction and maintenance therapy than placebo. (Funded by Pfizer; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain ClinicalTrials.gov numbers, NCT01465763, NCT01458951, and NCT01458574, respectively.)

Efficacy and Safety of Oral Tofacitinib as Maintenance Therapy for Moderate to Severe UC: OCTAVE Sustain Trial

- **593 UC patients**
- **Clinical response with induction phase**
- **Randomized to:**
  - **Placebo 198**
  - **Tofa 5 mg BID 198**
  - **Tofa 10 mg BID 197**
- **52 weeks**
- **1° endpoint: remission**
  - **Mayo Score ≤2**
  - **Bleeding score 0**
  - **No subscore >1**



Sandborn WJ *et al* UCSD LaJolla CA, USA oral #1080

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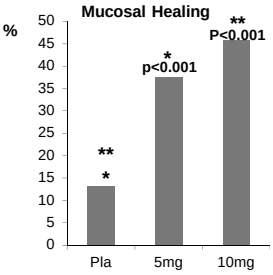

Sandborn WJ *et al* UCSD LaJolla DDW 2017 oral #1080

Tofacitinib Crohn's Disease

- **2 Randomized, double-blind, pacebo-controlled, multicenter, 2 dose trials.**
- **460 patients**
- **No statistical differences compared to placebo**

Panes J *et al* Gut 2017;66:1049-59

Janus Kinase (JAK) Inhibition

- **JAK phosphorylate activated cytokine receptors**
  - **Recruit STAT transcription**
- **Inhibitors block**
  - **IL-2, IL-4, IL-15, IL-21,**
  - **T_h2 cell differentiation**
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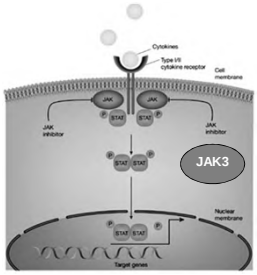
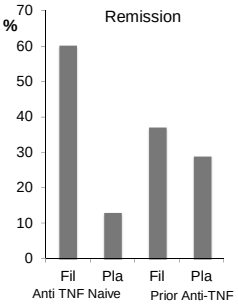


Filgotinib & Crohn's Disease

- **Selective JAK1 inhibitor**
- **52 centers in Europe**
- **174 pt, mod-severe disease**
- **Randomized**
  - **Filgotinib 200mg p.o.**
  - **Placebo**
- **Primary Outcome**
  - **Clinical remission at 10 weeks**



Vermeire S et al Lancet 2017; Jan 21: 266-75

Filgotinib
Fistulizing Crohn's Disease

- **Phase 2, Randomized, Placebo-controlled**
- **April 2017-May 2019**
- **75 patients**

ClinicalTrials.gov NCT03077412

Personalized Medicine

- **The right drug**
- **The right dose**
- **For the right patient**
- **At the right time**
- **Using the right route**

Ladak SS et al Pain Management Nurs 2007; 8: 140-5

The Right Dose
Therapeutic Drug Monitoring

	Minimum Therapeutic Trough Level
Inliliximab	3 µg/ml
Adalimumab ★	5 µg/ml
Vedolizumab	15 µg/ml
Ustekinumab	0-8-1.4 µg/ml

Personalized Medicine

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The Right Patient
High Risk Crohn's Disease

- **Young age at disease onset**
- **Fistulizing / stricturing disease**
  - **Fistula at 1st presentation**
- **Perianal disease**
- **Cigarette smoking**
- **Foregut disease**
- **Early post-operative recurrence**

Mosli M *et al* Amer J Gastro 2014; 109: 994-1994

Personalized Medicine

- The right drug
- The right dose
- For the right patient
- At the right time
- Using the right route

Ladak SS et al Pain Management Nurs 2007; 8: 140-5

At the Right Time

- Prior to:
  - growth impairment
  - fixed strictures
  - loss of continence

Personalized Medicine

- The right drug
- The right dose
- For the right patient
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- Using the right route

Ladak SS et al Pain Management Nurs 2007; 8: 140-5

The Right Route

- Dependability of the patient
- Practicality of i.v. infusions
  - Expense
  - Distance to an infusion center

The Right Biologic Conclusions

- None of the current biologics are superior for every patient with IBD
- Criteria to select the optimal biologic for a patient are not yet well-defined
- The clinician's choice of a biologic for a specific should take into account:
  - Past treatments
  - Pregnancy
  - Co-morbidities
  - Patient compliance