Antibodies and Levels of Biologics – Reactive vs. Proactive Measurements

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Conflict of Interest Disclosure

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Preview

- Reactive testing of drug concentration and antibodies vs. empiric dose escalation
- Proactive therapeutic drug concentration monitoring (TDM)
  - TAXIT
  - DDW 2014

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Anti-TNFs for Crohn's Disease

Infliximab (Remicade)	Placebo (n=110)	5mg/kg (n=113)	10mg/kg (n=112)
Remission at 30 weeks, %	21	39	45
Median time to LOR, wk	19	38	>54

Adalimumab (Humira)	Placebo (n=170)	Every other week (n=172)	Weekly (n=157)
Remission at 26 weeks, %	17	40[a]	47[a,b]
Remission at 56 weeks, %	12	36[a]	41[a,b]

Certolizumab pegol (Cimzia)	Placebo (n=101)	Certolizumab pegol (n=112)	*P*
Remission at 26 weeks,%	26	42	.01

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Sandborn WJ, et al. N Engl J Med. 2007;357(3):228-238.
Colombel JF, et al. *Gastroenterology.* 2007;132(1):52-65.

Patient

- 23 male with 2 years of Crohn's ileocolitis on infliximab 5mg/kg and azathioprine presents 6 weeks after his last infliximab dose with worsening abdominal pain, diarrhea, and weight loss.
- PE: Tenderness in right lower quadrant
- Labs: CRP 30, HCT 32; stool studies are negative
- Imaging: MRe confirms active disease
- What is the next step?
  - Increase infliximab 10mg/kg?
  - Decrease interval of infliximab to every 6 weeks?
  - Check infliximab concentration and antibodies to infliximab (ATI)?

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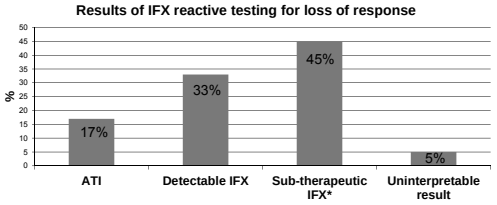
Most infliximab concentration and ATI testing done reactively

- Most common reason for testing is loss of response (49%)[1]



*Undetectable trough or < 12 at week 4

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[1]Afif et al. *Am J Gastroenterol* 2010;105:1133-1139

Measurement of IFX Conentration and ATI

Test results impacted treatment in 73 % of patients

Subtherapeutic IFX	Dose escalation	Complete or partial response - 86%
Subtherapeutic IFX	Switch anti-TNF	Response - 33%
Therapeutic IFX		No evidence of active inflammation in 62% of the patients
ATI positive	Switch anti-TNF	Response - 92%
ATI positive	Dose escalation	Response - 17%

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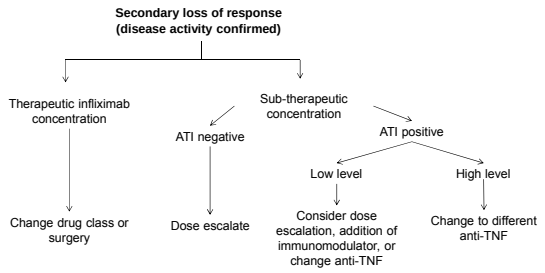
Afif W, et al. *Am J Gastroenterol.* 2010;105(5):1133-9.

Reactive testing algorithm



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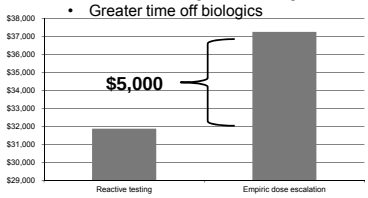
Adapted from Khanna et al. AP&T 2013; 38:447-459

Reactive testing is cost effective

- Compared to empiric dose escalation for secondary loss of response[1]
  - Reactive testing yielded similar QALYs
  - Similar rates of remission and response
  - Reactive testing was less expensive
    - Lower use of high-dose biologics
    - Greater time off biologics



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[1]Velayos et al. *Clin Gastronetol Hepatol* 2013;11:654-666

Reactive testing

- Confirm active IBD!
- Avoids dose intensification in those who will not benefit from more drug
- Allows targeted dose intensification in those whose loss of response is due to low drug concentration
- Directs patients with non-TNF driven disease to other therapeutic options

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Patient

- 23 male with 2 years of Crohn's ileocolitis doing well on infliximab 5mg/kg for the last 4 months
- Should you check his IFX trough concentration and ATI?

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Therapeutic drug monitoring – Proactive monitoring

- Commonly performed in other situations
  - Cyclosporine, mycophenolate, and mTOR inhibitors in solid organ transplantation[1]
  - Cyclosporine and tacrolimus use in UC[2,3]
  - Vancomycin and gentamycin in sepsis[4,5]
- Therapeutic window
  - Low concentrations result in lack of efficacy
  - High concentrations can result in increased toxicity
  - Biologics – immunogenicity*

[1]Monchaud C et al. Clin Pharmacokinet 2009;48:419–62
[2]Van Assche G et al. Gastroenterology 2003;125:1025–31.
[3]Ziring DA et al. J Pediatr Gastroenterol Nutr 2007;45:306–11.
[4]Zelenitsky S et al. Int J Antimicrob Agents 2013;41:255–60.
[5]Hansen M et al. Acta Anaesthesiologica Scandinavica 2001;45:734–40.

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Infliximab trough concentrations correlate with outcome

Crohn's disease

Trough level	Outcome
Detectable	Clinical remission, CRP, endoscopic remission[1]
> 3.5 ug/ml	Sustained response[2]
> 3 ug/ml	Sustained response[3]
> 5.6 mg/L	Lower CRP[4]
Undetectable	Loss of response[5]

Ulcerative Colitis

Trough level	Outcome
> 7.19 ug/ml	Sustained response[6]
Detectable	Increased rate of remission, endoscopic improvement[7]

[1]Maser et al. Clin Gastroenterol and Hepatol 2006;4(10):1248–54
[2]Cornillie et al. Gut 2014 [Epub ahead of print]
[3]Bortlik et al. Journal of Crohn's and Colitis 2013;7(9):736–43
[4]Lamblin et al. J Crohn's and Colitis 2012 p334
[5]Drobe et al. Gastroenterology 2011 p279
[6]Arias et al. Journal of Crohn's and Colitis 2012 OP10
[7]Seow et al. Gut 2010; 59:49-54

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Drug concentration monitoring correlates with outcomes for other biologics

- Adalimumab
  - Serum concentration > 5ug/ml predicted normal CRP and remission of Crohn's disease[1]
  - Low concentrations (median 2.5ug/ml) associated with drug discontinuation[2]
- Certolizumab Pegol
  - Week 8 and week 54 certolizumab levels correlated with endoscopic remission[3]

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[1]Mazor et al. ECCO 2013. P517
[2]Karmiris et al. *Gastroenterol* 2009;137:1628-1640
[3]Colombel et al. Clin Gastroenterol and Hepatol 2014;12:423-31

Proactive testing in IBD

- Trough level Adapted infliXImab Treatment (TAXIT) trial.
- Patients: Infliximab maintenance therapy with stable clinical response
- All patients underwent infliximab dose optimization to trough level of 3-7ug/ml
- Randomized to:
  - Infliximab dosing based on clinical symptoms and CRP
  - Infliximab dosing based on trough concentration
- Primary outcome: Clinical remission at 1 year

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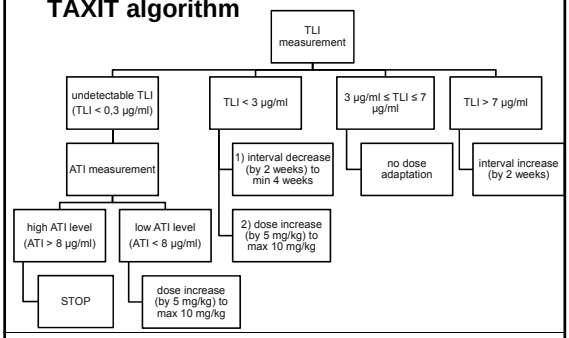
[1]*Vande Casteele et al. UEG Week Berlin 2013*

TAXIT algorithm



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[1]Vande Casteele et al. UEG Week Berlin 2013

TAXIT

Infliximab trough levels

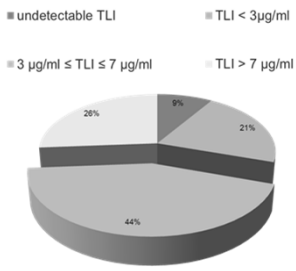

Figure: infliximab trough level (TLI) at time of screening (n=275)

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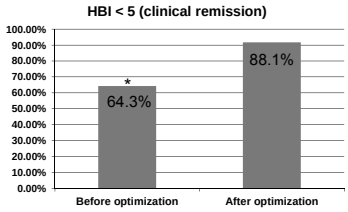
[1]Vande Casteele et al. UEG Week Berlin 2013

TAXIT results

- Dose escalation for Crohn's disease improved disease control



*p=0.02

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[1]Vande Casteele et al. UEG Week Berlin 2013

TAXIT results

- Primary endpoint - 1 year after optimization:
  - No difference in remission rates between concentration dosed and clinically dosed groups (p=0.77)
- Secondary endpoint:
  - Concentration-dosed group needed rescue therapy less frequently than clinically dosed group
    - 5.5% vs. 17.3% (p=0.004)
  - Non-significant trend towards fewer acute infusion reactions
- Similar cost between both groups

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[1]Vande Casteele et al. UEG Week Berlin 2013

TAXIT: Recommendations

1. Dose optimize to achieve IFX trough levels within interval 3-7 µg/ml
2. Re-evaluate levels after 6 months

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[1]Vande Casteele et al. UEG Week Berlin 2013

Hypothesis

- Monitoring and titrating infliximab trough concentrations to a target range of 5–10ug/ml will:
  - Increase the durability of infliximab
  - Decrease loss of response
  - Decrease immunogenicity
  - Potentially decrease infusion reactions
  - Potentially decrease adverse events

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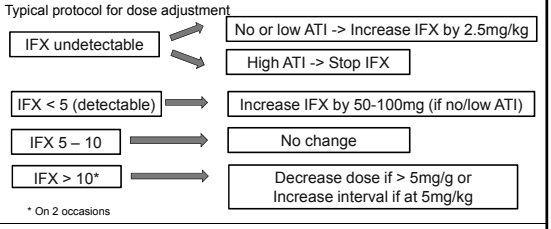
Vaughn B, et al, DDW 2014

Methods

Study group

- Retrospective cohort
- In 2009 one IBD attending began proactively monitoring infliximab serum concentrations and ATI

Typical protocol for dose adjustment



* On 2 occasions

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Methods

Study group

- Identified patients from IBD center who had infliximab concentration testing (Prometheus Laboratories)

- Exclusion criteria
  - Infliximab infusion not at BIDMC
  - Infliximab drawn from cord blood
  - No follow-up after concentration
  - Infliximab concentration not documented in GI note
  - No maintenance infusions
- Chart review:
  - Infliximab concentration and ATI
  - Clinical remission*
  - Intent: reactive or proactive
  - Changes to infliximab dosing
  - Duration of infliximab
  - Reason for infliximab discontinuation

*defined by the treated physician

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Methods

Control group (No TDM)

- Patients on infliximab in clinical remission*
- No proactive therapeutic drug monitoring
  - May have had reactive testing
- Received standard of care at discretion of treating MD
  - Empiric dose escalation or reactive testing for symptoms.
- Charts reviewed:
  - Demographics
  - Duration of infliximab
  - Reason for infliximab discontinuation

*defined by the treated physician

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Methods

Outcomes

- Duration of infliximab
  - Time-to-event curve (log rank test)
  - Censored at last clinical encounter that patient was receiving IFX or on 8/1/2013
- Infliximab discontinuation
- Infliximab trough concentrations
- Infliximab dosing changes

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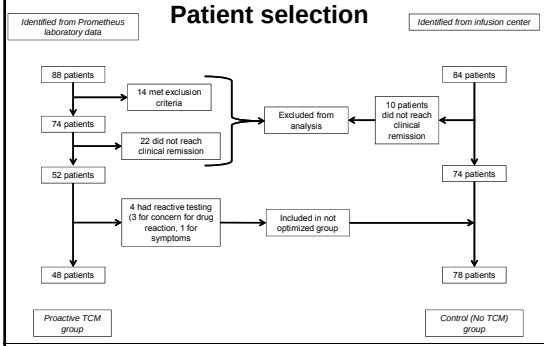
Results

Patient selection



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Results

Characteristic	TCM (%)	Control (%)	p value
Number of patients	48	78	
Gender			0.2
Male	33 (69)	45 (58)	
Female	15 (31)	33 (42)	
Median age at IFX initiation (IQR)	35 (29,42.5)	34.9 (26.2,49.7)	0.9
Disease			0.2
Crohn's disease	38 (79)	52 (67)	
Ulcerative colitis	10 (21)	24 (31)	
IBD-Unclassified	0	2 (3)	
Median age at Diagnosis (IQR)	23.5 (19.3,28)	25 (19.5,36.5)	0.3
Disease location			
Crohn's disease			0.1
Ileocolonic	24 (63.2)	26 (50)	
Ileum	9 (23.7)	10 (19.2)	
Colon	5 (13.2)	18 (34.6)	
Perianal	16 (42)	19 (36.5)	0.7
Ulcerative colitis			0.8
Extensive/Pancolitis	6 (60)	13 (54.2)	
Left sided	4 (40)	11 (45.8)	
Prior IBD Surgery	19 (40)	19 (25)	0.08
Tobacco status			0.6
Current	5 (10)	7 (9)	
Former	12 (25)	14 (18)	
Never	31 (56)	57 (73)	
Combination Therapy	21 (44)	31 (40)	0.7

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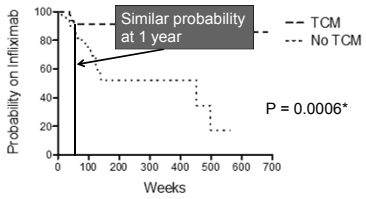
Results

Therapeutic concentration monitoring results in a longer duration of infliximab



Number at risk

TCM	48	34	16	10	5	4	2
No TCM	78	29	10	5	3	2	

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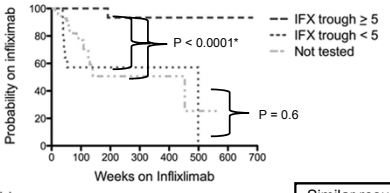
Results

Patients who achieved a trough concentration ≥ 5 ug/ml had a longer duration on infliximab



Number at risk

IFX trough ≥ 5	37	29	14	9	4	4	2
IFX trough < 5	15	8	5	3	3		
Not tested	74	27	8	4	3	2	

Similar results seen with cut off of 3ug/ml

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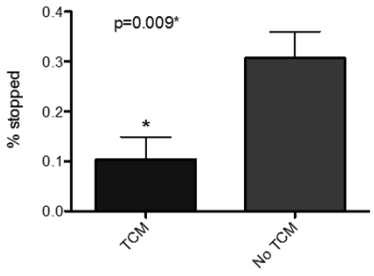
Results

Infliximab discontinuation



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Results

Reasons for infliximab discontinuation

	Optimized	Not Optimized
Ongoing IBD symptoms	0	15
Adverse events		
Pneumonia	0	1
Drug induced lupus	1	0
Psoriasis	1	0
High antibody (ATI) level	1	0
Infusion reactions		
Acute infusion reaction	0	6
Delayed infusion reaction	1	0
Other (unrelated to infliximab)*	1	2

73% of controls underwent dose escalation
¾ increased IFX 10mg/kg

*Includes: unable to afford co-payment, surgery for adhesive small bowl obstruction, colectomy for flat low-grade dysplasia.

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Results

Infliximab levels: Proactively monitored group

Trough cut off (ug/ml)	First trough concentration* n (%)	Subsequent trough concentration* n (%)
IFX undetectable	6 (24)	2 (4)
IFX trough concentration < 3	10 (40)	6 (11)
IFX trough concentration < 5	16 (64)	17 (30)
IFX trough concentration 5-10	5 (20)	21 (38)
IFX trough concentration > 10	4 (16)	20 (36)

*Reactive infliximab concentrations were excluded

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Results

Infliximab changes

	First trough concentration* n (%)	Subsequent trough concentration* n (%)
Change	11 (44)	14 (25)
Escalation of therapy	9 (82)	9 (64)
Decrease of therapy	0	5 (36)
Stopped therapy	2 (18)	0

*Changes based on reactive infliximab concentrations were excluded

Median IFX dose increase was 100mg (range 50 - 200mg)

14.6% patients de-escalated therapy (reduced dose or stopped)

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Limitations

- Study:
  - Retrospective
  - Single center
  - Potential residual confounding between two groups
- Practice
  - Potential cost to patient

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Summary: therapeutic drug monitoring

- Proactive infliximab concentration monitoring with dose optimization was associated with:
  - longer duration on infliximab
  - less infliximab discontinuation
- Initial trough concentrations were frequently low
- Benefit of trough monitoring is likely to be seen after 1 year
- Needs to be validated in a prospective study

We recommend dose optimization to at least 3 ug/ml
- Our current clinical practice is 5 – 10 ug/ml

Vaughn B, et al, DDW 2014

How are we different than TAXIT[1]

- All patients in TAXIT were dose optimized to 3-7ug/ml prior to randomization
  - Clinical scores improved after dose optimization for those with infliximab concentration <3ug/ml
- TAXIT had 1 year follow-up
  - Similar duration of infliximab in our study at 1 year between both groups

[1]*Vande Casteele et al. UEG Week Berlin 2013*

Background

Further benefits of therapeutic drug monitoring

- Can we obviate the need for combination therapy?
  - Initial treatment
  - De-escalate to monotherapy

Monotherapy  Combination therapy

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Background

Debate – Anti-TNF monotherapy or combination with immunomodulator

- Early studies did not show improved clinical outcomes with combination therapy
- Immunomodulators decrease the immunogenicity of anti-TNF
- Risks of combination therapy
  - Hepatosplenic T-cell lymphoma
  - Opportunistic infections
- Combination therapy with IFX and AZA more effective in treatment-naïve patients (SONIC and UC-SUCCESS)
- Immunomodulators increase anti-TNF trough levels and decrease ATI

Rutgeerts et al. N Engl J Med 2005;353:2462-76
Lichtenstein et al. Aliment Pharmacol Ther 2009;30:210-26
Vermeire et al. Gut;2007:56:1226-1231

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Hanauer et al. The Lancet 2005;359(9317):1541–9\
Rosh et al. Inflamm Bowel Dis 2007;13:1024-1030
Toruner et al. Gastroenterol 2008;134:929-36
Colombel et al. *N Engl J Med* 2010;365(15):1383-1395
Panaccione et al. Gastroenterol 2014;146:392-400

Background

What is the benefit of combination therapy?

- Is the benefit from combination therapy related to increased infliximab trough and decreased antibody formation?
- Can we achieve the same clinical benefit with titration of infliximab as monotherapy?

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Hypothesis

"Optimized monotherapy" is an alternative treatment strategy to combination therapy

- Proactive therapeutic infliximab trough concentration monitoring
- Titration to concentration level
  - Preferably 5-10 ug/dl
- Continued monitoring at regular interval

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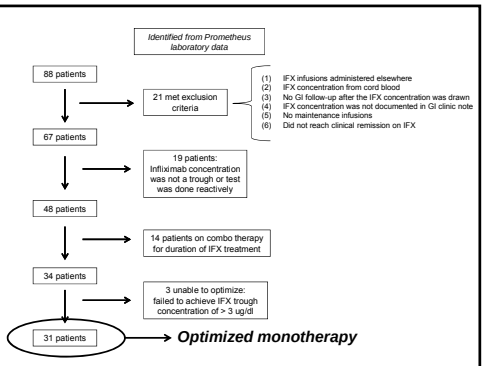
Results



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Results

Long term outcomes

- All patients eventually titrated to IFX trough concentration > 3 ug/ml
- 83% of patients achieved a trough concentration > 5 ug/ml
- No patient stopped infliximab at end of data collection
- Median follow-up time: 3.4 years

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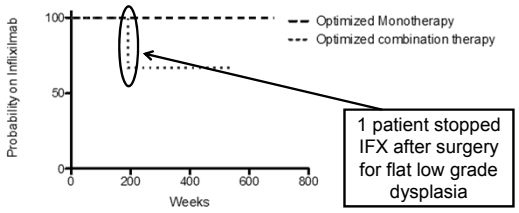
Similar duration of IFX between optimized monotherapy and combination therapy



Selecting for all patients who achieved a trough > 3ug/ml

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Results

De-escalating to monotherapy

Concentration on combination therapy (ug/ml)	Concentration off combination therapy (ug/ml)	Reason came off combination therapy
--	<1.4*	Patient concern re: AE of combo therapy
4.8	4.3*	Patient self discontinued
4.5	11.8	Went to surgery (appendicitis), remained on IFX only for post-op prophylaxis
9.4	--	Self discontinued
4.4	12.6	Patient concern re: AE of combo therapy
5.4	3.9*	Patient concern re: AE of combo therapy
--	3.8*	Disseminated VZV on combo
--	7.6	Patient concern re: AE of combo therapy

*Underwent infliximab dose escalation after stopping combination therapy

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Summary for optimized monotherapy

- Optimized monotherapy may be a feasible strategy for maintenance therapy with infliximab
  - Initial therapy?
  - De-escalation from combination therapy?
- If de-escalating from combination therapy, trough concentrations should be monitored when on monotherapy
- This strategy needs prospective validation

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Conclusions

- There is a positive association between biologic trough concentration and clinical response
- Currently drug monitoring is done reactively in IBD
  - More cost effective and directed therapy than empiric dose escalation
- Proactive dose optimization improved clinical scores and decreased need for rescue therapy (TAXIT) and prolonged duration of infliximab with less IFX discontinuation (Vaughn)
  - Benefit may be seen after 1 year
  - Optimized monotherapy may be alternative to combination therapy
- Issues – optimal trough concentration window; timing of testing; test that is accurate, accessible, and inexpensive; prospective data on implementation of TDM

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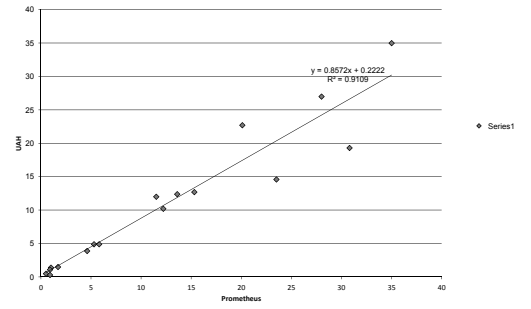
Alberta Elisa (Fedorak) vs. Prometheus



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