THE ROLE OF DRUG MONITORING IN INFLAMMATORY BOWEL DISEASE

Jennifer Strople, MD

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Ann & Robert H. Lurie Children's Hospital of Chicago

DISCLOSURES

- I have the following financial disclosures
  - Abbvie

OBJECTIVES

- 1. Understand the goals of TPMT testing and thiopurine metabolite monitoring in clinical care
- 2. Recognized the association between infliximab levels and clinical outcomes in UC and Crohn's disease
- 3. Interpret anti-TNF antibody levels and apply to patient care

PATIENT

- 16 y/o male with moderate/severe ileocolonic Crohn's disease
  - Mercaptopurine maintenance therapy (1 mg/kg dose)
- 6-TG level at 4 weeks subtherapeutic
  - Leukopenia with dose escalation
- Infliximab initiated
  - Good response initially, but develops breakthrough symptoms
  - Increased to 10 mg/kg q 6 weeks, no improvement
  - Transitioned to adalimumab

QUESTIONS

- Can therapeutic drug monitoring
  - Predict complications of mercaptopurine therapy?
  - Lead to optimization of medical therapy?
  - Prevent loss of response to anti-TNF therapy?
  - Improve patient outcome?

TPMT TESTING

- Goals: Minimize adverse effects, maximize clinical response
  - Prevent leukopenia, aggressively dose patients
- Polymorphisms in TPMT influence response
  - Normal/high activity (80-86%)
    - High TPMT may shunt to 6-MMPN
  - Low activity (10-14%)
    - Predictor of response and remission
  - Deficient (0.3%-0.6%)

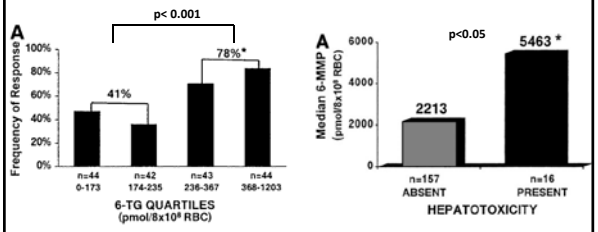
Dubinsky et al. Gastroenterology 2000;118:705
Ansari et al. Aliment Pharmacol Ther 2008;28:973
Cuffari et al. Clin Gastoenterol Hepatol 2004;2:410
Benkov et al. JPGN 2013;56:333

LIMITATIONS OF TESTING

- Myelosuppression occurs in patients with normal TPMT activity
  - 41 patients with leukopenia or thrombocytopenia
    - 30 (73%) normal TPMT alleles
    - 11 (27%) TPMT alleles associated with low activity
- No association of TPMT activity and hepatotoxicity
- Cannot predict other complications
- Cost effective?
  - Screening more cost effective than dose escalation based on lack of response

Columbel et al. Gastroenterology 2000;118:1025
Dubinsky et al. Gastroenterology 2002;122:903
Dubinsky et al. Am J Gastroenterol 2005;100:2239

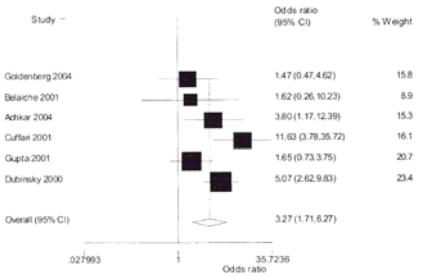
METABOLITE MONITORING



Therapeutic response 6-TG >235, OR 5

Dubinsky et al. Gastroenterology 2000;118:705

METABOLITE MONITORING



Patients with 6-TG level above 230-260 more likely to be in remission (OR 3.3)

Osterman et al. Gastroenterology 2006;130:1047

METABOLITE MONITORING

- Advantages:
  - Optimization of dose
  - Monitoring of noncompliance
  - Early identification of nonresponders
- Limitations:
  - Cost?
  - Over-interpretation of results

METABOLITE-DIRECTED ALGORITHM

6-TGN	6-MMP	Interpretation	Strategy
Therapeutic	Normal/High	Refractory, appropriately dosed	Change therapy
Low	Low/Normal	Underdosed Noncompliant	Increase dose Educate
High	Normal/High	Refractory, overdosed	Change therapy
Low	High	6-MMP shunter	Change therapy or add allopurinol

63 patients with active IBD:
Therapeutic levels both metabolites: 41%
Noncompliance: 10%
Underdosed: 29%
High levels both metabolites: 11%
Shunters: 10%

→

Algorithm +: 87% (40 of 46) improved
Alogrithm -: 18% (3 of 17) improved

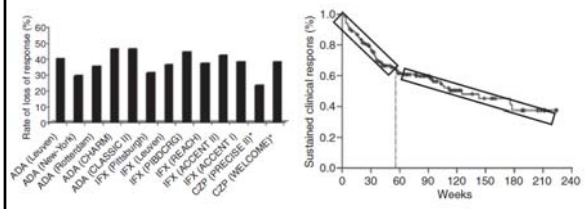
Haines et al. Inflamm Bowel Dis 2011;17:1301

CONSENSUS RECOMMENDATIONS

- TPMT testing is recommended before initiation of thiopurines
  - Homozygous recessive or low TPMT activity avoid thiopurines
  - TPMT testing does not predict all cases of leukopenia
- Role for metabolite testing to determine adherence or guide dose changes in patients with active disease
- Routine testing has no role in patients who are doing well on acceptable dose of thiopurines

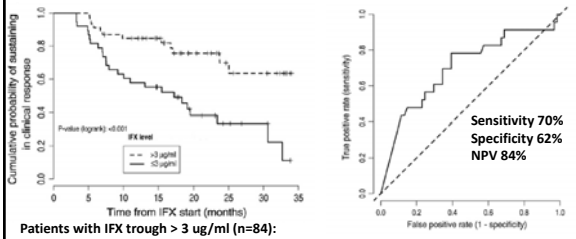
Benkov et al. JPGN 2013;56:333

LOSS OF RESPONSE TO ANTI-TNF THERAPIES



Ben-Horin, Aliment Pharmacol Ther 2011;33:987

IFX TROUGH PREDICTS SUSTAINED RESPONSE IN CROHN'S DISEASE



Patients with IFX trough > 3 ug/ml (n=84):

1. Lower mean CRP during maintenance phase
2. Longer sustained response (only predictor in multivariate analysis)

Loss of response to IFX at 1 yr by trough levels

ACCENT 1 (post hoc): Week 14 trough > 3.5 ug/mL predicted durable sustained response, OR 3.5, sensitivity 64%, specificity 78%, NPV 83%,

Bortlik et al J Crohns Colitis 2012;7:736
Cornillie et al. Gut 2014;63:1721

IFX TROUGH LEVELS-- PEDIATRIC IBD

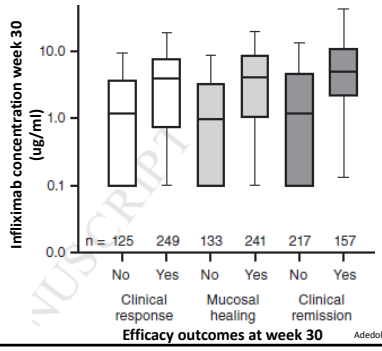
Week 14 IFX Levels and Outcomes (n=58)

Week 54 Outcome (Yes v. No)	Median IFX Level (ug/mL)
Persistent Remission	4.7 versus 2.6*
Clinical Remission	3.2 versus 2.2
Clinical & Laboratory Remission	4.2 versus 3.0
Sustained Durable Remission Week 14 to 54	5.5 versus 3.1*
Sustained Durable Remission Week 22 to 54	5.1 versus 3.0*

* p<0.05

Singh et al. Inflamm Bowl Disease 2014;20:1708

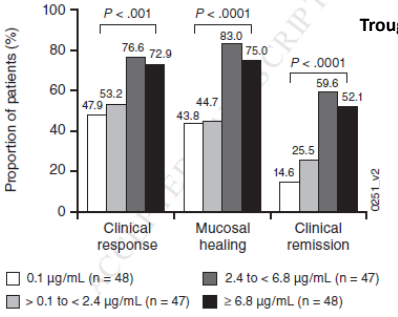
IFX CONCENTRATION AND OUTCOME IN ULCERATIVE COLITIS



Efficacy outcomes at week 30

Adedokun et al. Gastroenterology 2014

IFX CONCENTRATION AND OUTCOME IN ULCERATIVE COLITIS

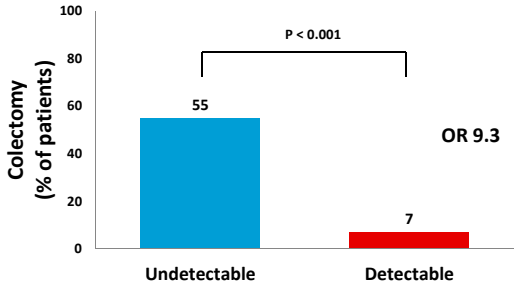


Trough >3.7 ug/ml optimal

Maintenance Week 30

Adedokun et al. Gastroenterology 2014

SERUM IFX TROUGH AND COLECTOMY IN UC



Seow et al. Gut 2010; 59:49-54

IFX TROUGH LEVEL AND 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]

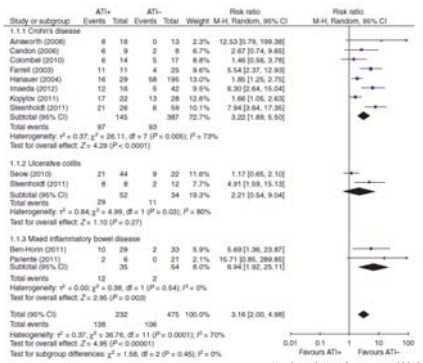
[1]Maser et al. Clin Gastroenterol and Hepatol 2006;4(10):1248–54
[2]Cornillie et al. Gut 2014 ; 63:1721
[3]Bortlik et al. Journal of Crohn's and Colitis 2013;7(9):736–43
[4]Lamblin et al. J Crohn's and Colitis 2012; 334
[5]Drobe et al. Gastroenterology 2011; 279
[6]Arias et al. Journal of Crohn's and Colitis 2012 OP10
[7]Seow et al. Gut 2010; 59:49-54

DRUG CONCENTRATION AND OUTCOMES

- **Adalimumab**
  - Serum concentration > 5 ug/ml predicted normal CRP and remission of Crohn's disease[1]
  - Level of 3 ug/ml discriminated between presence and absence of inflammation[2]
  - Low concentrations (median 2.5 ug/ml) associated with drug discontinuation[3]
- **Certolizumab Pegol**
  - Week 8 and week 54 certolizumab levels correlated with endoscopic remission[4]

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

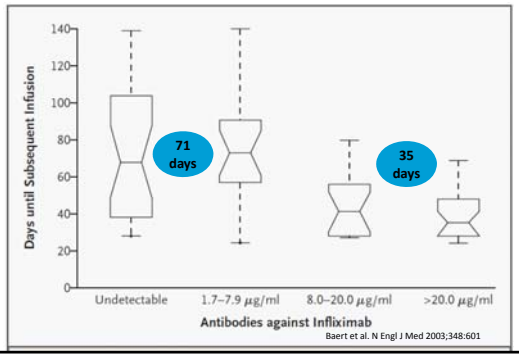
EFFECT OF ATI ON LOSS OF RESPONSE



RR 3.2

Nanda et al. Am J Gastroenterol 2013; 2013:40

DURATION OF RESPONSE BASED ON ATI LEVELS



Baert et al. N Engl J Med 2003;348:601

MEASUREMENT OF INFLIXIMAB CONCENTRATIONS AND ATI

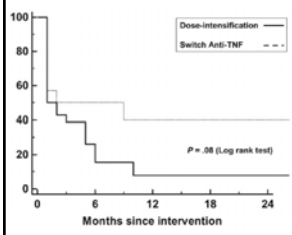
Test results impacted treatment in 73 % of patients

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%

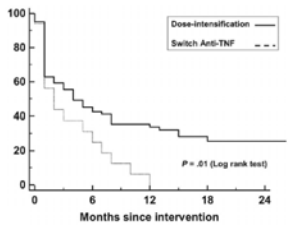
Afif W, et al. *Am J Gastroenterol.* 2010;105(5):1133-9.

ANTI-TNF DRUG/ANTIBODY LEVELS AND OUTCOME

Patients with high titer antibodies

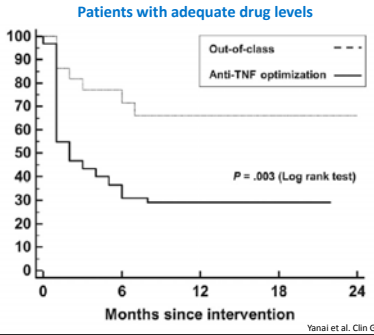


Patients with no/low titer antibodies



Yanai et al. Clin Gastroenterol Hepatol 2014

ANTI-TNF DRUG/ANTIBODY LEVELS AND OUTCOME



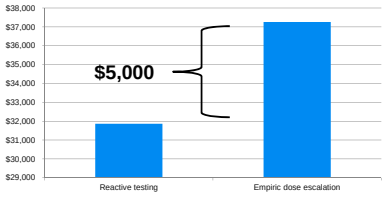
Yanai et al. Clin Gastroenterol Hepatol 2014

REACTIVE TESTING

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

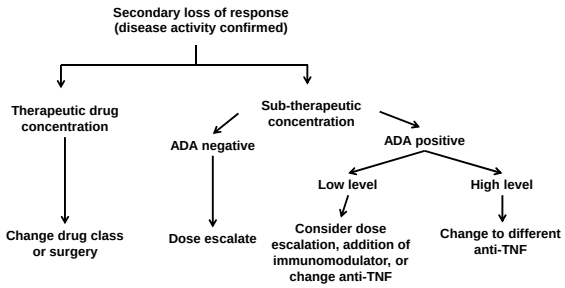
IS REACTIVE TESTING IS COST EFFECTIVE?

- 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



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

REACTIVE TESTING ALGORITHM



ADA—Anti drug antibody

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

SUMMARY

- There is a positive association between biologic trough levels and clinical response
- Evidence supports a role for drug monitoring in patients who have lost response to anti-TNFs
- Proactive monitoring may help optimize response
  - More research needed regarding optimal trough level and timing of testing