Inflammatory Bowel Disease: Biologic Therapeutic Drug Monitoring

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Disclosures

I have no relevant financial relationships or commercial interests to disclose for this presentation.

No pediatric specific information will be presented in this presentation.

Objectives

- Discuss the difference between pharmacodynamic and pharmacokinetic failure
- Describe the differences between immune-mediated and non-immune mediated pharmacokinetic failure

IBD Epidemiology

- Affects 1.5 million Americans
- 70,000 new cases each year

	Crohn's Disease (CD)	Ulcerative Colitis (UC)
Peak Incidence (years)	Bimodal 13-39 60-80	
Gender	Slight female predominance	Slight male predominance
Ethnicity	Jewish > Non-Jewish Caucasians > AA > Hispanics > Asians	

Nat Rev Gastroenterol. Hepatol 2015;12:205-17.

Complications

- Fistulas
  - 40%
- Abscesses
- Fissures (ulcer)
- Nutritional deficiencies
- Obstruction
- Stricture
- Intestinal resection
  - 60-80%
- Colon cancer risk (UC)

www.ibdrelief.com

Treatment Goals

- Induce and maintain remission of disease related symptoms
  - Including mucosal healing
- Maintain general well being while minimizing side effects and long term complications
- Reduce the need for long term corticosteroids
- Improve patient quality of life
- Minimize cancer risk (UC)

Am J Gastroenterol 2010;105:501-23.

Biologic Therapies

- Anti-TNFα
  - Infliximab
  - Adalimumab
  - Certolizumab
  - Golimumab
- Anti-IL-12/Anti-IL-23
  - Ustekinumab
- Leukocyte Adhesion Inhibitors
  - Vedolizumab
  - Natalizumab

Same Dose For All?

- Phenytoin
- Warfarin
- Vancomycin
- Aminoglycosides
- Digoxin
- Tacrolimus/Cyclosporine
- Everolimus/Sirolimus

Same Dose For All?

- Patient Factors:
  - Disease severity/Degree of inflammation
  - Phenotype
  - Use of immunomodulator
  - Patient sex (male)
  - Body mass index
  - Variability in drug clearance

Pharmacokinetics/ Pharmacodynamics

- Mechanistic failure
  - Unlikely to respond to other drugs within the same class
- Nonimmune-mediated pharmacokinetic failure
  - Rapid drug clearance
- Immune-mediated pharmacokinetic failure
  - Anti-drug antibodies

Aliment Pharmacol Ther. 2017;46:1037–1053.

Mechanistic Pharmacodynamic Failure

- The underlying process is through a different "pathway"
  - Molecular polymorphisms in apoptosis genes or other pathways
  - TNF-independent inflammatory pathways
- IBD is complex with a complicated pathophysiology
- Need to switch to medications that target other pathways
- Drug class is not effective

Aliment Pharmacol Ther. 2017;46:1037–1053.

Nonimmune-Mediated Pharmacokinetic Failure

- Absorption:
- Distribution:
  - Patient's body weight (weight based vs set doses)
  - Degree of systemic inflammation
- Metabolism: Variability in drug metabolism
- Elimination:
  - Degree of inflammation in GI tract

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Immune-Mediated Pharmacokinetic Failure

- Absorption
- Distribution
- Metabolism
  - Development of antibodies against biologic medications
  - Use of immunomodulator
- Elimination

Aliment Pharmacol Ther. 2017;46:1037–1053.

Questions

- Which of the following would best describe pharmacodynamic failure to biologic therapies for inflammatory bowel disease?
  a) Mechanistic failure to biologic therapy likely due to different mechanism of disease pathway
  b) Changes in the clearance of biologic therapy due to formation of antibodies against biologic therapy
  c) Differences in patient's body weight altering drug concentration
  d) All of the above

Therapeutic Drug Monitoring (TDM)

- TDM most often occurs in setting of loss of response to therapy
  - 23-46% at 12 months with anti-TNFa
- Defined as emerging symptoms as a result of inflammation associated with IBD
- Trough drug concentrations and ADAs can guide clinicians
- Rule out non-inflammatory mechanisms (irritable bowel syndrome, dietary factors)

Gastroenterol Hepatol 2013;11:444-7.

Therapeutic Drug Monitoring (TDM)

- Drug levels
  - Correlate with longer remission and better endoscopy scores
- Anti-drug antibodies
  - Decrease efficacy
  - Increase infusion or administration reactions
- Anti-drug antibodies (ADA) can develop with anti-TNFα after prolonged use
  - Incidence 9-17%

Gastroenterology 2009; 137:1628-40.

Therapeutic Drug Monitoring (TDM)

- Other instances
  - Pts reintroduced to anti-TNFα after drug holiday
    - Pregnancy, surgery, insurance issues, nonadherence
    - At higher risk of developing immunogenicity, infusion reactions, and loss of response

Gut 2016;65:1126-31.

Immunogenicity Negatively Influences the Outcomes of Adalimumab Treatment in Crohn's Disease

West RL, Zelinkova Z, et al.	
Study Design	Retrospective study in patients with Crohn's disease treated with adalimumab (n=30)
Objective	Assess if antibodies to adalimumab can affect treatment outcomes in patients with Crohn's disease previously treated with infliximab
Results	Median time before assessment of antibodies was 346 days, antibodies were detected in 5 patients (17%) and were related to nonresponse to adalimumab (OR 13.1, p=0.006) Serum antibodies were significantly increased in adalimumab nonresponders (163 v 520.4 p=0.01)
Conclusion	Antibodies to adalimumab effect treatment outcomes in patients with CD

Aliment Pharmacol Ther. 2008;28:1122–1126.

Influence of Trough Serum Levels and Immunogenicity on Long-term Outcome of Adalimumab Therapy in Crohn's Disease

Karmiris K, Paintaud G, et al.	
Study Design	Observational cohort study in patients with CD
Objective	Assess long term clinical benefit utilizing trough serum concentrations and antibodies against adalimumab in patients who failed to respond to infliximab
Results	Antibodies were present in 9.2% of patients Adalimumab trough concentrations <0.33 mcg/mL demonstrated significant less sustained clinical benefit (p=0.01) Higher discontinuation rates in patients with a trough serum concentration <0.094 mcg/mL (91.6%) compared to concentration >0.094 mcg/mL (40.7%) OR 16.0 p=0.001
Conclusion	Discontinuation was directly related to decreased adalimumab concentrations due to developing antibodies

Gastroenterology. 2009;137: 1628-1640.

Limitations To Studies

- The studies used to derive different target trough concentrations were cross-sectional studies of patients on maintenance therapy in various stages of clinical response or remission
- Studies were not specifically designed to identify optimal drug levels!

Role of Proactive TDM?

- TAXIT Study
  - TDM guided group had fewer flares needing steroid (7% vs 17%, p=0.018)
- TAILORIX Study
  - No benefit of proactive TDM
- Retrospective Study
  - Lower rates of treatment failure, hospitalization, surgery, development of anti-drug antibodies

Aliment Pharmacol Ther. 2017;46:1037–1053.

Goal Trough Levels

- Assays available for infliximab, adalimumab, golimumab, certolizumab pegol, vedolizumab and ustekinumab

Drug	Suggested trough concentration (ug/mL) American Gastroenterological Association	Suggested trough concentration (ug/mL) Consensus Statement
Infliximab	≥ 5	3-8
Adalimumab	≥ 7.5	5-12
Certolizumab pegol	≥ 20	No recommendation
Golimumab	Unknown	No recommendation
Vedolizumab	Unknown	No recommendation
Ustekinumab	Unknown	No recommendation

Gastroenterology 2017; 153:827-834.
Aliment Pharmacol Ther. 2017;46:1037–1053.

Suboptimal Drug Level

- Screen for anti-drug antibody (ADA)
- Negative ADA (non-immune mediated)
  - Shorten the drug-dosing interval and/or escalating the dose
- Positive ADA (immune mediated)
  - High-titer
    - Antibodies switching to a different drug within the same class may be more effective
  - Low-titer antibodies
    - May be transient and non-neutralizing
    - Shorten the drug-dosing interval and/or escalating the dose

Aliment Pharmacol Ther. 2017 Dec;46(11-12):1037-1053.

Optimal Drug Level

- Negative ADA
  - Consider switching out of drug class, concern for primary non-responder
- Positive ADA
  - Consider switching out of drug class, concern for primary non-responder

Aliment Pharmacol Ther. 2017 Dec;46(11-12):1037-1053.

Supraoptimal Drug Level

- Negative ADA
  - Consider switching out of drug class, concern for primary non-responder
- Positive ADA
  - Consider switching out of drug class, concern for primary non-responder

Aliment Pharmacol Ther. 2017 Dec;46(11-12):1037-1053.

Patient Case

OC is 43 year old male with CD following up in clinic after 6 months with persistent abdominal fullness and post-prandial abdominal discomfort, nausea, and intermittent vomiting - last vomiting was 1 weeks ago. He reports having 1-2 BMs daily with no blood in stools. Reports adherence to adalimumab every 2 weeks. Patient states that he does not feel like the adalimumab is making a difference with his symptoms.

Questions

- The gastroenterologist agrees with your plan to send the trough labs and a week later you receive the following lab results.
  - Adalimumab drug level 3.1 (goal 5-12)
  - Anti-adalimumab antibody undetectable
- What would you recommend regarding his current adalimumab therapy? Please provide route, dose and frequency?
  a) Keep the same regimen
  b) Increase adalimumab to 40 mg every week
  c) Decrease adalimumab to 40 mg every 4 weeks
  d) Discontinue therapy, patient is a primary non-responder

Summary

- IBD has no medical cure; drug therapy is the mainstay in inducing and maintaining remission
- There are intrinsic variations in the pharmacokinetics and pharmacodynamics of biologic therapies that can affect outcomes
- When to check TDM
  - Reintroduction after a drug holiday
  - Loss of response or no response to therapy
  - Proactive monitoring?

Questions?