Inflammatory Bowel Disease: Biologic Therapeutic Drug Monitoring

David Choi, PharmD, BCACP
Clinical Assistant Professor UIC
College of Pharmacy
Clinical Pharmacist, Transplant & GI

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 immunemediated 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)	<u>Bimodal</u> 13-39 60-80	
Gender	Slight female predominance	Slight male predominance
Ethnicity	Jewish > Non-Jewish Caucasians > AA > Hispanics > Asians	
Gastroenterol. Hepatol 2015;12:205-	17.	

Complications

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

ww.ibdrelief.c

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;46:1037–105

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

liment Pharmacol Ther. 2017;46:1037–105

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

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

Immune-Mediated Pharmacokinetic Failure

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

Aliment Pharmacol Ther. 2017;46:1037–1053

Questions

- Which of the following would best describe <u>pharmacodynamic failure</u> 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
 - 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 <u>loss of</u> 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)

Therapeutic Drug Monitoring (TDM)

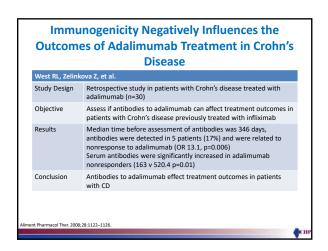
- Drug levels
 - Correlate with longer remission and better endoscopy scores
- Anti-drug antibodies
 - Decrease efficacy
 - Increase infusion or administration reactions
- Anti-drug antibodies (ADA) can develop with anti-TNF α after prolonged use
- Incidence 9-17%

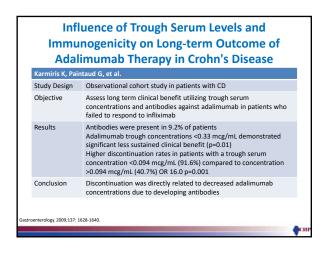
Gastroenterology 2009; 137:1628-40

Therapeutic Drug Monitoring (TDM)

- Other instances
 - Pts reintroduced to anti-TNF α 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





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

liment Pharmacol Ther. 2017;46:1037–1053

Goal Trough Levels Assays available for infliximab, adalimumab, golimumab, certolizumab pegol, vedolizumab and ustekinumab Suggested trough Suggested trough concentration (ug/mL) Consensus Statement concentration (ug/mL) American Gastroenterological Infliximab 3-8 > 5 <u>></u> 7.5 Certolizumab pegol <u>≥</u> 20 No recommendation Unknown Golimumab No recommendation Vedolizumab Unknown No recommendation Ustekinumah Unknown No recommendation

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

ment 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

liment Pharmacol Ther. 2017 Dec;46(11-12):1037-105

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?