Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.
MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.

ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

SPECIAL EDITION: GIQuIC QuiC Bite Webinar – Wednesday, September 28, 2022
Screening Colonoscopy Updates: What They Mean for Your Practice
Wednesday, September 28, 2022 at 8pm Eastern

Week 39 – Thursday, September 29, 2022
Diagnosis and Management of Cancer Risk in the Gastrointestinal Hamartomatous Polyposis Syndromes: Recommendations from the US Multi-Society Task Force on Colorectal Cancer
Faculty: Gregory E. Idos, MD
Moderator: Veroushka Ballester, MD
Thursday, September 29, 2022 at Noon Eastern and NEW! 8pm Eastern!

Visit gi.org/ACGVGR to Register
Disclosures

Andres J. Yarur, MD, FACG
Arena Pharmaceuticals: Consultant
Boehringer Ingelheim: Consultant
Bristol Myers Squibb: Consultant
Procise: Consultant

Ryan C. Ungaro, MD, MS
AbbVie: Advisory board, consultant
Bristol Myers Squibb: Advisory board, consultant
Janssen: Advisory board, consultant
Pfizer: Advisory board, consultant
Takeda: Advisory board, consultant

*All of the relevant financial relationships listed for these individuals have been mitigated
THERAPEUTIC DRUG MONITORING OF BIOLOGICS IN IBD: WHY, WHEN AND HOW?

Andres Yarur, MD FACG
Associate Professor of Medicine
Division of Gastroenterology
Cedars Sinai Medical Center
Los Angeles, California

GOAL

• Understand what is therapeutic drug monitoring of therapies in IBD
• Why can be an important tool
• Review when and how to use it
• Answer a lot of questions!
The NEW ENGLAND JOURNAL of MEDICINE

Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis


A HIGH NUMBER OF PATIENTS DO NOT RESPOND

Clinical remission in anti-TNFα naïve patients (ITT) (CDAI ≤ 150)
for Targan study CDAI < 150
REMISSION AT 4 WEEKS1,2,3

2. UCB Data on File.
A HIGH NUMBER OF PATIENTS DO NOT RESPOND

Vedolizumab in Crohn's Disease

Vedolizumab in UC

Ozanimod in UC

Ustekinumab in UC

Half Empty
CHALLENGES WITH BIOLOGIC THERAPY

• Of those who do respond…
• A significant amount lose response

17

PHARMACOKINETIC PRINCIPLES: THERAPEUTIC DRUG MONITORING IN IBD

18

AUC = area under the curve
$C_{\text{max}} =$ maximum concentration
$M_{\text{EC}} =$ minimum effective concentration
$M_{\text{TC}} =$ maximum tolerated concentration
$t_{\text{max}} =$ time to $C_{\text{max}}$.
OBSERVATIONS THAT LED TO THE DEVELOPMENT OF TDM IN BIOLOGIC THERAPY FOR IBD

EXPOSURE-RESPONSE: INFLIXIMAB

EXPOSURE-RESPONSE: ADA LIMUMAB

Higher adalimumab levels correlate with higher efficacy

Mucosal Inflammation
Mean ADA level 8.5 µg/mL

Endoscopic Healing
Mean ADA level 13.3 µg/mL

P=0.02

Yarur A et al. Inflamm Bowel Dis. 2016

EXPOSURE-RESPONSE OF VEDOLIZUMAB

Post-hoc Gemini study

Osterman et al. Aliment Pharmacol Ther. 2019
USTEKINUMAB.... SIMILAR STORY?

Battat et al. CGH 2017
Pancholi C et al. DDS 2020

Yarur et al. Presented at DDW 2022
THE ROLE OF PHARMACOKINETICS IN NON-RESPONSE TO BIOLOGICS: ANTI-TNF

Higher drug levels = higher efficacy
Let’s “fill the tank”

CLINICAL TRANSLATION OF THESE FINDINGS

Measuring Drug Levels and the Presence of Anti-Drug Antibodies
Use to Guide Therapeutic Decisions
**INCREASE IN INFliximab Levels is Associated with Better Clinical Outcomes**

- Observations that higher anti-IFX levels are associated with lower disease activity raised the question if increasing drug levels may lead to better outcomes.

- Dose-escalating patients with “low” drug levels translates only into a 50%-86% rate of response.

C. Steenholt et al. Journal of Crohn’s and Colitis, 2015

**Multiple Factors Affect the PK of Anti-TNF**

- Anti-Drug Antibodies
- Genetic Factors?
- Drug Clearance
- Inflammatory Burden
- Body Mass?
- Use of Immunomodulators
- Biologic Drug Levels
**IMMUNOGENICITY AGAINST ANTI-TNF BIOLOGICS IS PREVALENT**

<table>
<thead>
<tr>
<th>Biotherapeutic</th>
<th>Episodic Maintenance</th>
<th>Scheduled Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>38%</td>
<td>11%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>38%</td>
<td>11%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>No data</td>
<td>10%</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>No data</td>
<td>10%</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>24%</td>
<td>12%</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>No data</td>
<td>12%</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>No data</td>
<td>4%</td>
</tr>
<tr>
<td>Golimumab</td>
<td>No data</td>
<td>13.1%</td>
</tr>
</tbody>
</table>

ANTI-DRUG ANTIBODIES ARE ASSOCIATED WITH LOWER DRUG LEVELS AND WORSE OUTCOMES

\[ P < .01 \]

- ATI negative (n = 13) AUC 1361 mg/L/day
- ATI positive (n = 6) AUC 760 mg/L/day

ANTI-DRUG ANTIBODIES ARE BAD NEWS (AT LEAST IN ANTI-TNFS)… HOW CAN WE AVOID THEM?
CONCOMITANT USE OF IMMUNOMODULATORS

Patients, %

<table>
<thead>
<tr>
<th>Drug</th>
<th>Episodic Maintenance</th>
<th>Scheduled Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMS-</td>
<td>IMS+</td>
</tr>
<tr>
<td>Infliximab(^1)</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>(CD 5 mg/kg)</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>(CD 10 mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab(^2)</td>
<td>19%</td>
<td>9%</td>
</tr>
<tr>
<td>(UC 5 mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(UC 10 mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certolizumab(^3)</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>(PRECISE I)</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Certolizumab(^4)</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>(PRECISE II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab(^5)</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>(RA, all doses)</td>
<td>12%</td>
<td>1%</td>
</tr>
<tr>
<td>Adalimumab(^6)</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>(CLASSIC II)</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Golimumab(^7)</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>(RA)</td>
<td>13.1%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>


CONCOMITANT USE OF IMMUNOMODULATORS

- The concomitant use of immunomodulators are associated with higher anti-TNF drug levels and lower rate of anti-drug antibodies
  - Thiopurines
  - Methotrexate
Using Combination Therapy with a Second Anti-TNF After Immune-Mediator Loss of Response to a First Anti-TNF


Infliximab + Azathioprine Associated with Better Pharmacokinetic Profile

* Among patients with CD and similar serum concentrations of infliximab, combination therapy with azathioprine was not significantly more effective than infliximab monotherapy.
GENETICS
HLA-DQA1*05 CARRIAGE ASSOCIATED WITH IMMUNOGENICITY TO INFLIXIMAB AND ADALIMUMAB

IMMUNOGENICITY IN VEDOLIZUMAB AND USTEKINUMAB

- The prevalence of anti-vedolizumab antibodies is lower than in Anti-TNF: 3-5%
- GEMINI I: 3.7%
- GEMINI II: 4.1%
- Similar with Ustekinumab (2.3% in UNITI)
- Most of them are transient and have no clinical significance

Yanu A et al. DDS 2021
Ward MG et al. Ther Adv Gastro 2018
HOW ABOUT THERAPEUTIC DRUG MONITORING FOR THIOPURINES?

METABOLISM OF THIOPURINES

- Complex and not completely understood
THIOPURINE METABOLITES

- 6-TGN has been the metabolite most associated with treatment efficacy.
- Its measurement has been proposed as a strategy to optimize treatment in patients with IBD receiving AZA/6-MP.
- 6-TGN level >230 pmol/8 x 10^8 RBC has been correlated with clinical remission.

Osterman MT, Gastroenterology. 2006;130:1047–1053.

MEASURING THIOPURINE METABOLITES

- Non-response to monotherapy
- Compliance
- High liver enzymes
COMBINATION THERAPY IMPROVES THE PHARMACOKINETICS OF ANTI-TNF AGENTS AND THIOPURINE SUB-METABOLITES ARE ASSOCIATED WITH EFFICACY.

HOW ABOUT IF WE USE THIOPURINE METABOLITES TO GUIDE COMBINATION THERAPY?

HIGHER 6-TGN IMPROVE THE PK OF INFLIXIMAB.

*Yarur et al. Presented at DDW 2022*
HIGHER 6-TGN DO NOT IMPROVE THE PK OF VEDOLIZUMAB

Yarur et al. Presented at DDW 2022

HIGHER 6-TGN DO NOT IMPROVE THE PK OF USTEKINUMAB

Yarur et al. Presented at DDW 2022
WHEN TO PERFORM THERAPEUTIC DRUG MONITORING
THE PROACTIVE VS REACTIVE DEBATE

USE OF REACTIVE THERAPEUTIC DRUG MONITORING WITH BIOLOGICS
REACTIVE TDM

• Recommended after primary or secondary non-response
• Scenarios when to use reactive TDM:

**Active Clinical Disease**

**AND/OR**

**High biomarkers**

**Active endoscopic disease**

PATIENTS WITH LOSS OF RESPONSE ANTI-TNF

- Measurement of anti-TNF level and anti-drug antibodies

  - Undetectable or low anti-TNF level and (-) ADA
    - Increase anti-TNF dose or decrease infusion interval
  - High anti-TNF level and (+) or (-) ADA
    - Switch to another drug class
  - Undetectable or low anti-TNF level and (+) ADA
    - High ADA level
      - Switch anti-TNF or Drug Class
    - Low ADA level
      - Dose optimization and consider adding IMM
    - No response

Yarur AJ & Rubin DT. Inflamm Bowel Dis. 2015 Jul;21(7):1709-182015
HOW ABOUT REACTIVE TDM WITH VEDOLIZUMAB?

EXPOSURE-RESPONSE IN VEDOLIZUMAB

Yarur et al. DDS 2019

Yarur et al. DDS 2019
ASSOCIATION DOES NOT IMPLY CAUSATION

ENTERPRET Study: Increasing drug exposure in non-responders with HIGH drug clearance

Moderate to Severe UC
Starting Vedolizumab

Participants with mucosal healing at week 30, (%)

Endoscopic mucosal healing at week 30
Mayo endoscopic subscore ≤ 1 by centrally read examination

*Modified so a score of 1 does not include friability.
REACTIVE TDM: USTEKINUMAB

• The evidence is limited
• Antibodies are rare
• Common practice of increasing the dose
  ○ What is really a low level?

BUT IS PROACTIVE TDM REALLY BETTER?
AVOID UNDER-EXPOSURE TO INFILIXIMAB

- Avoid under-exposure to infliximab
- IFX levels < 3 mcg/dL
- “pseudoepisodic treatment”

DOES IT MAKE SENSE TO BE PRO-ACTIVE?
PRO-ACTIVE VS REACTIVE TDM WITH INFliximab


PRO-ACTIVE TDM WITH INFliximab: NORDRUM

- RCT- open label: Pro-active TDM vs. standard therapy

<table>
<thead>
<tr>
<th>Disease subgroup</th>
<th>Remission rate, No./total (%)</th>
<th>Therapeutic drug monitoring</th>
<th>Standard therapy</th>
<th>Adjusted difference, % (95% CI)</th>
<th>Favors therapeutic drug monitoring</th>
<th>Favors standard therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>21/38 (55.3)</td>
<td>21/42 (50.0)</td>
<td>-8.3 (-30.4 to 13.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>5/10 (50.0)</td>
<td>12/22 (54.5)</td>
<td>29.4 (-0.2 to 59.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spondylarthrits</td>
<td>23/39 (59.0)</td>
<td>21/58 (36.2)</td>
<td>-3.5 (-21.4 to 14.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>25/39 (64.1)</td>
<td>29/41 (70.7)</td>
<td>4.9 (-15.6 to 25.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn disease</td>
<td>17/29 (58.6)</td>
<td>17/28 (60.7)</td>
<td>4.7 (-21.1 to 30.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td>9/13 (69.2)</td>
<td>6/9 (66.7)</td>
<td>-8.3 (-47.7 to 31.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>100/198 (50.5)</td>
<td>106/200 (53.0)</td>
<td>1.5 (-8.2 to 11.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Watterdal Syversen et al. JAMA. 2021;325(17):1744-1754
PRO-ACTIVE VS REACTIVE TDM WITH ADALIMUMAB

• Adalimumab-level-based optimization treatment in a multicenter, nonblinded trial
• Primary endpoint: sustained steroid-free clinical remission (PCDAI<10) from Weeks 8 to 72
• Proactive trough measurements + tight control based superior to reactive trough measurements + tight control
• Goal ADA level >5 mcg/ml

PRO-ACTIVE TDM WITH BIOLOGICS: ANTI-TNF PRACTICAL IMPLICATIONS

• Consider in patients on anti-TNF, especially in:
  ✓ High drug clearance and/or severe disease
  ✓ Monotherapy
  ✓ After reactive TDM
  ✓ After anti-TNF dose reduction

• No evidence for pro-active TDM in biologics other than anti-TNF
Multiple studies show multiple “target: threshold levels”

The truth is there is no “magic number”

Multiple variables can affect these targets:

- Assay used in studies can be heterogeneous
- Different phenotypes may require different targets
- Especially with adalimumab, tissue levels not always correlate with serum levels.
PRO-ACTIVE TDM WITH ANTI-TNF: WHERE TO AIM?

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Measurement Timepoint</th>
<th>Goal (mcg/mL)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Week 2</td>
<td>&gt;15-20</td>
<td>Clinical Remission at Week 14</td>
</tr>
<tr>
<td></td>
<td>Week 14</td>
<td>&gt;12</td>
<td>Mucosal Healing week 30</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>&gt; 8-10</td>
<td>Normal Calprotectin Week 14</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>&gt;20</td>
<td>Fistula healing</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Maintenance</td>
<td>&gt;8</td>
<td>Mucosal Healing</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>&gt;10</td>
<td>Fistula closure</td>
</tr>
</tbody>
</table>

**PRACTICAL RECOMMENDATIONS ON DRUG LEVEL TARGETS?**

- **Aim high**
- **Do not “give up” on anti-TNF if the dose can be escalated as long as there are no antibodies**
- **Some phenotypes may benefit from really “high” doses**

---

Yarur A et al. AP&T 2017
RE-STARTING TREATMENT AFTER A DRUG HOLIDAY

• Not uncommon
• Infliximab in the past may have not been optimized
• Known high risk of immunogenicity after re-exposure

  • Non-response
  • Infusion reaction

HOW TO USE TDM WHEN RE-STARTING INFLEXIMAB

Normatov I, et al. Crohns Colitis 360. 2021

American College of Gastroenterology
IN SUMMARY (I)

• Reactive drug monitoring is
  ▪ Helpful when using anti-TNF
  ▪ May be “too late” if just relying on symptoms
  ▪ Reactive is not just for symptoms

• Have a monitoring strategy and don’t rely only on symptoms
  ✓ Biomarkers
  ✓ Endoscopy

• Incorporate TDM in treat-to-target strategies

IN SUMMARY (II)

• Evidence is limited but “makes sense” to use pro-active TDM with Anti-TNF, especially on:
  ✓ Aggressive disease
  ✓ Re-starting treatment with infliximab

• Vedolizumab and ustekinumab have very low immunogenicity and the significance of serum drug levels is not completely understood

• Just because TDM is useful with anti-TNF doesn’t mean is useful with other biologics
Questions and Answers

Andres J. Yarur, MD, FACG

Ryan C. Ungaro, MD, MS
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