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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.

ACG Virtual Grand Rounds
Join us for upcoming Virtual Grand Rounds!

Week 26 – June 30, 2022
Geriatrics and Gastrointestinal Disorders: Is Age Only a Number?
Bharati Kochar, MD, MS
June 23, 2022 at Noon Eastern and NEW! 8pm Eastern!

Week 28 – July 14, 2022
Fertility, Preconception, and Pregnancy in IBD
Eugenia Schmidt, MD
July 14, 2022 at Noon Eastern and NEW! 8pm Eastern!

Visit gi.org/ACGVGR to Register
Biologics in IBD: Western Perspectives

Stephen B. Hanauer, MD
Professor of Medicine,
Northwestern University
Feinberg School of Medicine
Medical Director, Digestive Health Center
What have we learned from TNFi and Other Biologic Clinical Trials?

• Effective for treatment of Crohn’s and UC
• All mABs are immunogenic
• High-dose induction, regular maintenance & immunomodulators reduce immunogenicity
• Combination therapy is more efficacious than monotherapy*
• Loss of response may be due to immunogenicity, pharmacology, or loss of mechanism
• Risks include infections and neoplasia & are increased with steroids & thiopurines


Room for Improvement With TNF Inhibitors in UC

Results presented here are from individual clinical trials and not from head-to-head trials. Therefore, no comparisons should be made between different agents.

Induction efficacy was reported at Week 8 for infliximab and adalimumab and Week 6 for golimumab and vedolizumab.

Maintenance efficacy was reported at Week 52 for infliximab and adalimumab, Week 54 for golimumab, and Week 52 for vedolizumab and golimumab.

Evidence for combination therapy in Crohn’s Disease in immunosuppressive-naive patients: SONIC

Corticosteroid-free clinical remission at Week 26

Proportion of patients (%)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Week 26 Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA+ placebo</td>
<td>30.0</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>44.4</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>56.8</td>
</tr>
</tbody>
</table>

Colombel JF, et al. NEJM 2010; 362:1383-95

UC Combination Therapy With a Thiopurine Is More Efficacious Than Infliximab Monotherapy

Mucosal Healing at Week 16

Δ = 8.28; P = 0.295

Δ = 25.98; P = 0.001

Patients With Mucosal Healing at wk 16, % (95% CI)

Δ = 17.70; P = 0.028

Starting Anti-TNF Therapy: The Importance of Timing


VICTORY: Disease Duration Impacts Steroid-Free Remission and Endoscopic Remission in Crohn’s Disease

Patients with CD for ≤2 years are significantly more likely to achieve a corticosteroid-free remission or endoscopic remission to VDZ than patients with longer disease duration.

CD: Crohn’s disease; VDZ: vedolizumab.
Phenotypic Features of Crohn’s Disease Associated with Anti-TNF Treatment Failure

Probability of surgery over time after anti-TNF prescription depending on phenotype at prescription
Retrospective study using the Alberta IBD Consortium Registry

Vedolizumab vs Adalimumab in Moderate-Severe UC
VARSITY: Mucosal Healing Week 52

Mucosal healing defined as endoscopic Mayo score ≤1.

Combination Therapy Does Not Improve Clinical/Endoscopic Remissions with Vedolizumab or Ustekinumab in CD and UC

- Ustekinumab initiated in CD patients (n=291)
  - 44% on combination therapy with thiopurine/MTX
- Vedolizumab initiated in 381 patients (203 CD, 178 UC)
  - 25% on combination therapy with thiopurine/MTX
- Patients followed with DAIs (HBI, SCCAI, or pMayo Score)
- Primary outcomes were clinical remission or response at 14, 30, and 54 weeks

Kaplan-Meier survival curve comparing monotherapy vs combination therapy

Hu A et al. Clin Gastroentrol Hepatol 2020 Jul 12;S1542-3565(20)30973-3 (online)

Ustekinumab Associated With Superior Effectiveness Compared With Vedolizumab in CD With Prior TNFi

- Patients achieving combined corticosteroid-free clinical and biochemical remission
  - Vedolizumab (n=69)
  - Ustekinumab (n=69)

Cumulative drug survival

Biemans VBC et al. Aliment Pharmacol Ther. 2020;00:1–12.
Adalimumab vs Ustekinumab for Moderate-Severe Crohn’s (Seavue)

Primary Endpoint:
Clinical Remission (CDAI<150) at Week 52

\[ \Delta = 4.0\% \text{ (95\% CI: -5.5\%, 13.5\%)} \]
\[ p=0.417 \]

Percent of Patients (%)

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab</th>
<th>Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61.0</td>
<td>64.9</td>
</tr>
<tr>
<td>Patients</td>
<td>119/195</td>
<td>124/191</td>
</tr>
</tbody>
</table>

Late Breaking Abstract DDW 2021

Anti-TNF Agents: When and How to Use Them

Advantage of anti-TNF agents

- Severe UC (infliximab)
- Rapidity of action
- EIM, independent from disease activity (PG, AS, uveitis)
- Associated RA, HS
- Pregnancy safety data

Limitations of anti-TNF agents

- Infectious risk
- Reactivation of Hep B, TB
- Need for IMM (at least year 1)
  - ↑ Infectious and lymphoma risk
- Contraindications: MS, CHF, etc.
- h/o lymphoma, active malignancy
- No live virus vaccines

AS, ankylosing spondylitis; CHF, congestive heart failure; EIM, extraintestinal manifestations; HS, hidradenitis suppurativa; IMM, immune modulator; PG, pyoderma gangrenosum; RA, rheumatoid arthritis; TB, tuberculosis

Improving Initial Response to Biologics

• Treat earlier in course (before complications)
  – Impeded by Access
• Ensure “Complete Response”
  – Treat to Target
• Combination Therapy
  – Infliximab/Adalimumab
  – Ustekinumab?/Vedolizumab?
• Consider PK/PD
  – Factors contributing to high clearance
• Utilize Therapeutic Drug Monitoring
  – Prospective TDM remains to be established

Key Safety Considerations with IBD Therapies

Cytopenias
  Anti-TNF
  Thiopurines
  Methotrexate

Heart failure
  Anti-TNF

Hepatotoxicity
  Anti-TNF
  Thiopurines
  Methotrexate

Osteoporosis
  Corticosteroids

Infection
  Anti-TNF
  Corticosteroids
  Thiopurines
  Tofacitinib

Malignancy
  Anti-TNF
  Corticosteroids
  Thiopurines

Immunogenicity
  Anti-TNF
  Vedolizumab

Note: Prescribing information from the following products contain a boxed warning: Anti-TNF agents (serious infections and malignancy), tofacitinib (serious infections and malignancy), methotrexate (bone marrow, lung, and kidney toxicities); and thiopurines (malignancy).

Positioning Therapies in Moderate to Severe IBD

**TNF antagonists**
- IV vs SC options
- Rapid onset of action (IV hospitalized patients)
- Best with immunomodulator
- Infection risk
- Lymphoma risk (with immunomodulator)

**Lymphocyte trafficking (Vedolizumab)**
- IV option (SC?)
- Low rate of immunogenicity
- Onset of action?
- Better results in TNF naïve patients
- Monotherapy or combination therapy?
- “Gut-Selective”
- Long-term safety

**Anti-IL12/23 (Ustekinumab)**
- Similar induction success as TNFi agents
- Efficacy in TNF- naïve and -failure patients
- Safety superior to anti-TNF therapies
- Low rate of immunogenicity
- Good use if concomitant psoriasis

**JAK inhibitors (Tofacitinib, Upadacitinib)**
- Oral
- Rapid onset of action
- Monotherapy, indicated after anti-TNF failure
- Maintenance dosing vs transition?
- Infection risk (zoster)
- MACE
- Lymphoma

**S1P Modulator (Ozanimod, Etrasimod)**
- Oral
- Rapid onset of action
- Monotherapy
- Dose-Titration
- Cardiac conduction

---

**Positioning Therapies in IBD**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Strongly Consider</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe inpatient</td>
<td>IFX or cyclosporine to VDZ</td>
<td>Fast onset of action, Weight-based dosing, TDM</td>
</tr>
<tr>
<td>Traveler, values convenience of injections</td>
<td>USK or ADA</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>VDZ or USK</td>
<td>Safety</td>
</tr>
<tr>
<td>Immunosuppressed, post-transplant</td>
<td>VDZ or USK</td>
<td>Safety</td>
</tr>
<tr>
<td>Lymphoma, melanoma</td>
<td>VDZ or USK</td>
<td>Safety</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>Often none needed during chemo. VDZ or USK</td>
<td>Anti-TNF does not increase risk of recurrence</td>
</tr>
<tr>
<td>Diffuse EIM</td>
<td>Anti-TNF</td>
<td>Systemic</td>
</tr>
</tbody>
</table>

ADA, adalimumab; EIM, extraintestinal manifestation; USK, ustekinumab; VDZ, vedolizumab.
Inadequate Treatment Leads to Serious Consequences

Flare and hospitalization
Up to 25% of patients are hospitalized for severe UC

Colorectal cancer
2.4-fold greater risk in patients with UC

Colectomy
≈ 30% of patients require colectomy; significant morbidity, persistent QoL issues

Cardiovascular disease
Increased risk of MI, stroke, CV mortality—especially during flares


Signature Cytokines and Their Functions in the Inflammatory Process of Arthritis and Colitis

Current and Emerging Strategies for IBD


Comments on Biologics for IBD

- Despite “humanness” they are all immunogenic
  - Immunogenicity is reduced by Immune suppressants…..
- Anticipate dose adjustment with all
- There will be diminishing returns with 2\textsuperscript{nd} and/or 3\textsuperscript{rd} agent
  - Duration of Disease
  - Refractory Disease
  - Immunogenicity
Biosimilars in the West

- Biosimilars are highly similar to originator biologic products
  - They cannot be considered generic biologics
  - Designed to decrease medication costs and increased access to treatment
- Biosimilar TNF inhibitors are now available for the treatment of adults with IBD
- Interchangeability is a critical issue for patients and physicians that bears careful monitoring
  - Currently, only one biosimilar has interchangeable designation
  - Third-party payers may mandate switches or initiation of biosimilar
- Transitioning patients to biosimilars
  - Educate
  - Allow patient time to make decision
  - Requires multidisciplinary approach to ensure best outcomes

Status of Biosimilars for IBD in the United States

- Adalimumab biosimilars
  - Abrilada™ (adalimumab-afzb) – November 2019
  - Hadlima (adalimumab-bwwd) – July 2019
  - Hymiroz (Adalimumab-adaz) – October 2018
  - CYLTEZO™ (Adalimumab-adbm) – August 2017
  - AMJEVITA™ (Adalimumab-atto) – September 2016
- Infliximab biosimilars
  - IXIFI™ (Infliximab-qbtx) – December 2017
  - RENFLEXIS® (Infliximab-abda) – April 2017
  - INFLECTRA™ (Infliximab-dyyb) – April 2016
The Future of IBD Therapy


Selection of therapy
- Treat-to-target: No symptoms and mucosal healing
- Tight control: Frequent reassessment/PK monitoring/objective disease monitoring

New predictive tools
- Omics, serologic markers, serum and fecal biomarkers

High risk patients
- Early combination therapy

Low risk patients
- Rapid step-up therapy

Predicting response to therapy
- Determining who needs early surgery?

High risk patients
- Early combination therapy

Low risk patients
- Rapid step-up therapy

Assess disease severity

Predict disease course

Current proposed management strategies
Future personalized management strategies


Biologicals in IBD: Indian Perspective

Vineet Ahuja
Department of Gastroenterology
All India Institute of Medical Sciences, New Delhi
The first five questions which a patient asks:

1. Is it the right time to start biologicals?
2. Is the biosimilar going to be as effective?
3. Anti TNF leads to TB reactivation, how to avoid it?
4. Are biologicals going to be life long?
5. Can a short course of biologicals work?
Earlier Anti-TNF Initiation Leads to Long-term Lower Health Care Utilization in Crohn’s Disease but not in Ulcerative Colitis

Laura E. Targownik,1* Charles N. Bernstein,2* Eric L. Benchimol1,3,4,5,9,11
Gilaad G. Kaplan,6 Harminder Singh,5,6 Aruni Tennakoon,6 Zoann Nugent,6
Stephanie B. Coward,9 M. Ellen Kuenzig,9 and Sanjay K. Murthy1,3,7,9

742 CD cases

- Anti-TNFs within 2 years of diagnosis had lower health care utilization in the subsequent 5 years

318 UC cases

- The same effect was not seen in UC cases


Shorter Disease Duration Is Associated With Higher Rates of Response to Vedolizumab in Patients With Crohn’s Disease but Not Ulcerative Colitis

David M. Faleck,3,5,6 Adam Winters,3 Shreyya Chablaney,3,6 Preeti Shashi,3 Joseph Meserve,6 Aaron Weiss,6 Satimai Aniwat,3,6 Jenna L. Kolianni-Pace,6 Gurimnan Kochhar,1 Brigid S. Boland,3,6 Siddharth Singh,3,6,7 Robert Hirten,3

650 CD cases

- Patients with CD for 2 years or less are significantly more likely to achieve a complete response

437 UC cases

- Disease duration does not associate with response vedolizumab in patients with UC

Clinical Gastroenterology and Hepatology 2019;17:2497–2505
Relationships between short disease duration and better outcomes was found in Crohn’s Disease but NOT in Ulcerative Colitis

Is it the right time to start biologicals?

Early use of biologicals may provide an advantage in Crohn’s Disease but this effect is not seen in Ulcerative Colitis
Is the biosimilar going to be as effective?

Adalimumab biosimilar in usual clinical practice is safe and effective in inducing and maintaining remission

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crohn's disease (n=49)</th>
<th>Ulcerative colitis (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant medications while starting biologics²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>12 (24.5%)</td>
<td>7 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>5-ASA</td>
<td>8 (16.3%)</td>
<td>9 (42.8%)</td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>19 (38.7%)</td>
<td>6 (28.5%)</td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>5 (10.2%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Response CDAI³ &gt; 100, SCCAI&lt;3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 weeks</td>
<td>28 (57.1%)</td>
<td>13 (61.9%)</td>
<td>0.67</td>
</tr>
<tr>
<td>20 weeks</td>
<td>21 (42.8%)</td>
<td>10 (47.6%)</td>
<td>0.59</td>
</tr>
<tr>
<td>52 weeks</td>
<td>18 (36.7%)</td>
<td>8 (38.1%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Remission CDAI&lt;150, SCCAI≤2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 weeks</td>
<td>23 (46.9%)</td>
<td>11 (52.4%)</td>
<td>0.71</td>
</tr>
<tr>
<td>26 weeks</td>
<td>20 (40.8%)</td>
<td>9 (42.8%)</td>
<td>0.71</td>
</tr>
<tr>
<td>52 weeks</td>
<td>16 (32.6%)</td>
<td>7 (33.3%)</td>
<td>0.91</td>
</tr>
</tbody>
</table>
Efficacy and safety of biosimilar versus originator infliximab in patients with inflammatory bowel disease: a real-world cohort analysis

137 patients (82 CD; 55 UC)
102 : Remicade
35 : Biosimilar IFX

Infliximab biosimilar is comparable to originator infliximab in terms of safety profile and its efficacy

Kumar P, et al IJG 2022

Anti TNF leads to TB reactivation, how to avoid it?
The risk of TB is proportional to local TB incidence, being highest in high TB burden countries, and is independent of disease (CD vs UC) or treatment type (IFX vs ADA)

Am J Gastroenterol 2020

Stringent screening strategy significantly reduces reactivation rates of tuberculosis in patients with inflammatory bowel disease on anti-TNF therapy in tuberculosis endemic region

Am J Gastroenterol 2020

Stringent Latent TB Screening

Liberal Chemoprophylaxis

- Latent TB positive

CT chest: evidence of old TB, calcification >5mm, pleural thickening, upper lobe fibronodular disease.
A cohort comparison was done to evaluate for risk reduction of TB following the stringent screening strategy.

Jan 2019-Dec 2020 (Cohort A) • 59 patients on anti TNF with stringent screening strategy

2005-Dec 2018 (Cohort B) • 112 patients on anti TNF

Risk reduction of TB from 17% to 1.7%.

TB reactivation risk can be significantly mitigated with stringent LTB screening and LTB prophylaxis.

Stringent Latent TB Screening

- Any of screening test positive
  - TST
  - IGRA
  - CECT Chest
  - Past history of TB

Liberal Chemoprophylaxis

- Latent TB positive
- CT chest: evidence of old TB, calcification >5mm, pleural thickening, upper lobe fibronodular disease

Risk reduction of TB from 17% to 1.7%.
Is biological therapy going to be life long?

- When a patient is in clinical and mucosal remission after receiving biologicals for 1 year or more
  - Continue Azathioprine/methotrexate
  - 40-50% relapse rate at 1 and 2 years
  - Most relapses occur within 6-12 months
  - Retreatment with biologicals is Safe and Successful
  - Groups where relapse rate high: Perianal, Complicated or relapsing disease, Previous dose escalation, Longer disease duration
  - De-escalation is a case-by-case decision and should be shared with the patient
44 of the 78 perianal CD patients (56.4%) relapsed after stopping anti-TNF

- More than half of the perianal CD patients developed relapse after stopping anti-TNF therapy. Most regained response after resuming anti-TNF.
- Radiological assessment before stopping anti-TNF is crucial in perianal CD

Can a short course of biologics work?
Maintaining infliximab induced clinical remission with azathioprine and 5-aminosalicylates in acute severe steroid-refractory ulcerative colitis has lower cost and high efficacy (MIRACLE): a multicenter study

Ramtii Mahajan 1, Arshdeep Singh 1, Saurabh Kadla 2, Kirandeep Kaur 2, Vandana Mishra 3, Pabitra Sahu 2, Varun Mehta 1, Dharmatma Singh 3, Namita Bansal 4, Khushdeep Dharm 5, Sandeep Kaushal 3, Vineet Ahuja 2, Ajit Sood 1

IFX (5 mg/kg intravenously at weeks 0, 2, 6) had been used only as an induction therapy and thereafter maintained with AZA/5ASA

137 patients: 77 (56.2%) achieved clinical remission
Cumulative corticosteroid-free remission in
60% at 2 years
35% at 6 years

Minimal risk of lymphoma and non-melanoma skin cancer despite long-term use of thiopurines in patients with inflammatory bowel disease: A longitudinal cohort analysis from northern India

Mukesh Kumar Ranjan 1, Bhaskar Kante 1, Sudheer Kumar Vuyyuru 1, Peeyush Kumar 1,

- 1093 patients (788 UC; 305 CD)
- 254 patients > 5 years thiopurines
- 68 patients > 10 years thiopurines
- No patient developed lymphoma or non-melanoma skin cancer
Predictors of Non Response to Anti-TNF Therapy

**Disease-related factors**
- Long duration of disease
- Initial non-response to anti-TNF treatment
- Smoking
- Strictureing disease

**Drug related factors**
- Inadequate drug levels
- Anti-drug antibodies
- Hypoalbuminemia
- High TNF tissue burden

**Oncostatin M drives intestinal inflammation and predicts response to tumor necrosis factor–neutralizing therapy in patients with inflammatory bowel disease**

North Indian Cohort: 186 patients
Predictors of primary non-response in patients on biologicals (anti-TNF)

<table>
<thead>
<tr>
<th>Crohn’s Disease</th>
<th>Univariate HR(95%CI)</th>
<th>P Value</th>
<th>Multivariate HR(95%CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>118 patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>0.075(0.02-0.2)</td>
<td>&lt;0.001</td>
<td>0.04(0.002-0.90)</td>
<td>0.04</td>
</tr>
<tr>
<td>Post Op Recurrence</td>
<td>5.24(1.8-14.5)</td>
<td>0.001</td>
<td>0.95(0.51-18.01)</td>
<td>0.31</td>
</tr>
<tr>
<td>IL-7R</td>
<td>1.5(1.04-2.15)</td>
<td>0.027</td>
<td>1.49(0.86-2.56)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UC</th>
<th>Univariate HR(95%CI)</th>
<th>P Value</th>
<th>Multivariate HR(95%CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>68 patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>0.07(0.03-0.20)</td>
<td>&lt;0.001</td>
<td>0.58(0.006-0.5)</td>
<td>0.012</td>
</tr>
<tr>
<td>CRP</td>
<td>1.18(1.07-1.29)</td>
<td>&lt;0.001</td>
<td>1.03(0.97-1.09)</td>
<td>0.31</td>
</tr>
<tr>
<td>Oncostatin M</td>
<td>1.87(1.18-2.95)</td>
<td>0.007</td>
<td>1.3(0.76-2.3)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

- EEN is effective both as an adjunct and as well as the only treatment in inducing remission
- Approximately 2/3rd experience clinical response by 8 weeks
- Oligomeric as well as polymeric formulas provide similar benefit
Are Crohn’s disease strictures responsive to drug therapy?

Real world analysis on the efficacy and safety of anti-tumor necrosis factor therapy in patients with stricturing Crohn’s disease

Cumulative success rate at 12 months: 69%
Cumulative success rate at 24 months: 51%
Cumulative success rate at 60 months: 28%
Intensive drug therapy versus standard drug therapy for symptomatic intestinal Crohn's disease strictures (STRIDENT): an open-label, single-centre, randomised controlled trial

Julien D Schulberg, Emily K Wright, Bente A Holt, Amy L Hamilton, Tom R Sutherland, Alyson L Ross, Sara Vagin, Ashley M Milles, William C Cennell, Mark Lost, Nik S Ding, Gregory T Moore, Sally J Bell, Edward Shenton, Brit Christensen, Peter De Cruz, Yuwei J Rong, Michael A Kamm

Intensive dose arm
- Adalimumab 160 mg every week for four weeks
- Adalimumab 40 mg every 2 weeks + Thiopurines
- Treat to target with dose escalation 12 months

Standard Dose arm
- Adalimumab 160 mg Week 0
- 80 mg Week 2
- Adalimumab 40 mg every 2 weeks + Thiopurines
- No treat to target approach

www.thelancet.com/gastrohep Vol 7 April 2022

Crohn’s disease strictures are responsive to drug therapy
Most patients in both treatment groups had symptom improvement
Intensification of therapy resulted in fewer patients failing treatment

www.thelancet.com/gastrohep Vol 7 April 2022
Treating fistulizing Crohn’s Disease with Biologicals
Infection  Inflammation

Antibiotics

Drain Perianal abscess

Seton Thread

Top Down Therapy

Biologics

Azathioprine

Long-term outcomes of anti-tumor necrosis factor therapy and surgery in nonperianal fistulizing Crohn's disease

Sudheer K Vuyyuru 1, Devendra Desai 2, Saurabh Kedia 3, Pavan Dhole 2, Pabitra Sahu 1, Bhaskar Kanit 1, Samagra Agarwal 3, Sawan Bopanna 1, Rajan Dhangra 1, Pratap Mouli Venigalla 1, Raju Sharma 3, Siddhartha Datta Gupta 4, Govind Makharia 1, Peush Sahni 5, Vineet Ahuja 3

Anti-TNF therapy appears to be as effective as and it may be indicated in the absence of abscess and other complications
**Short-term anti-TNF therapy with surgical closure versus anti-TNF therapy in the treatment of perianal fistulas in Crohn's disease (PISA-II): a patient preference randomised trial**

Elise M Meima-van Praag, Kees L van Bij, Karin A T G M Wasmans, Harmen A Snijder, Jaap Stoker, Gert I Oerman, Kristlina R Gots, Michael F Gerhards, Jeroen M Jansen, Merel G W Dijkgraaf, Jarmila D W van der Bilt, Marco W Mundt, Antonino Spinelli, Siikko Donner, Willem A Rempelman, Christianne J Buiteman

Active high perianal fistula with a single internal opening

4-month anti-TNF therapy and surgical closure

Anti-TNF therapy for 1 year, after seton insertion

**Primary outcome**: Radiological healing assessed by MRI at 18 months

<table>
<thead>
<tr>
<th></th>
<th>Surgery +anti TNF N=38</th>
<th>Anti TNF N=56</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologic healing at 18 months</td>
<td>12(32%)</td>
<td>5(9%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Clinical closure</td>
<td>26(68%)</td>
<td>29(52%)</td>
<td>0.079</td>
</tr>
</tbody>
</table>

Lancet Gastroenterol Hepatol. 2022 Jul;7(7):617-626

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**Can you add one biological to another biological/small molecule?**
### Virtual Grand Rounds

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>IBD subtype (n)</th>
<th>Type of combination therapy</th>
<th>Clinical remission (%)</th>
<th>Infectious adverse events (%)</th>
<th>Median duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buer (2018)</td>
<td>Prospective observational</td>
<td>CD (4) UC (6)</td>
<td>ADA/IFX + VDZ</td>
<td>80</td>
<td>30</td>
<td>6 months</td>
</tr>
<tr>
<td>Glassner (2020)</td>
<td>Retrospective</td>
<td>CD (31) UC (18)</td>
<td>VDZ + TOFA VDX + anti-TNF anti-TNF + TOFA TOFA + UST ADA + APR</td>
<td>50</td>
<td>34</td>
<td>8 months</td>
</tr>
<tr>
<td>Alayo (2021)</td>
<td>Retrospective</td>
<td>CD (25) UC (10)</td>
<td>TOFA + VDZ TOFA + IFX TOFA + UST</td>
<td>10.7</td>
<td>2.8</td>
<td>4 months</td>
</tr>
<tr>
<td>Yang (2020)</td>
<td>Retrospective</td>
<td>CD (22)</td>
<td>VDZ+ anti-TNF UST + anti-TNF UST + VDZ</td>
<td>41</td>
<td>NA</td>
<td>9 months</td>
</tr>
<tr>
<td>Goessens (2021)</td>
<td>Retrospective</td>
<td>CD (58) UC (40)</td>
<td>VDZ + TOFA VDX + anti-TNF anti-TNF + TOFA TOFA + UST UST + VDZ UST + anti-TNF</td>
<td>26</td>
<td>10</td>
<td>8 months</td>
</tr>
</tbody>
</table>

( Kamar S, et al., Curr Opin Gastro 2022 in review)
**Patient’s perspectives**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is it the right time to start biologicals?</td>
<td>Early initiation in CD may be helpful but not in UC</td>
</tr>
<tr>
<td>Is the biosimilar going to be as effective?</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti TNF leads to TB reactivation, how to avoid it?</td>
<td>Stringent screening and liberal chemoprophylaxis Prev h/o TB very important</td>
</tr>
<tr>
<td>Are biologicals going to be life long?</td>
<td>50% relapse rates at 1-2 years after stopping Azathioprine maintenance therapy helps</td>
</tr>
</tbody>
</table>

**Physician’s perspectives**

| Predictors of success of biological therapy | Serum Albumin a very strong predictor |
| CD stricturing disease                     | Yes, responsive to biologicals         |
|                                          | Avoid if large prestenotic dilatation  |
| Perianal Fistulizing therapy               | Adjunct therapy: Seton + antibiotics + |
|                                          | Immunomodulators very important        |
| Dual Biological therapy                    | In very select cases a possible modality |

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**Panel Discussion**

**Questions and Answers**

- **Mahesh K. Goenka, MD, FACG**
  - Moderator

- **Govind K. Makharia, MD, DM, DNB**

- **Samir A. Shah, MD, FACG**

- **Rakesh Kochhar, MBBS, MD**
  - Moderator

- **Ajit Sood, MD, DM**