WHY HAVE WE NOT FINALLY FIGURED OUT COMBINATION THERAPY?

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Objectives

1. Become aware of evidence and best practice in clinical trials and “real world” for combination therapy: adalimumab, infliximab, vedolizumab, and ustekinumab

2. Understand why some biologics perform better in combination

3. Review state-of-the-art and recent data from ECCO and DDW abstracts
How to optimize benefit from anti-TNF?

- Right TIME
- Right PATIENT
- Stop SMOKING
- Use BIOLOGIC LEVELS to guide secondary non-response and dose de-escalation
- COMBINATION therapy with azathioprine or methotrexate
Monotherapy versus Combination Therapy: Biologic and IM

• Rationale for Combination Therapy
  – Independent effect of a 2nd drug
  – Synergistic effects of two drugs
  – Lower rates of anti drug antibody formation
  – Lower rates of infusion reactions and loss of response
  – Higher drug levels, better clinical outcomes

• Rationale for Monotherapy
  – Safety concerns of combination therapy

Many factors influence individual anti-TNF pharmacokinetics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact on TNF antagonist PK</th>
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<tbody>
<tr>
<td>Presence of ADAs</td>
<td>Decreases drug concentration</td>
</tr>
<tr>
<td></td>
<td>Increases clearance</td>
</tr>
<tr>
<td></td>
<td>Worse clinical outcomes</td>
</tr>
<tr>
<td>Concomitant use of immunosuppressives</td>
<td>Reduces ADA formation</td>
</tr>
<tr>
<td></td>
<td>Increases drug concentration</td>
</tr>
<tr>
<td></td>
<td>Decreases drug clearance</td>
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<tr>
<td></td>
<td>Better clinical outcomes</td>
</tr>
<tr>
<td>Low serum albumin concentration</td>
<td>Increases drug clearance</td>
</tr>
<tr>
<td></td>
<td>Worse clinical outcome</td>
</tr>
<tr>
<td>High baseline CRP concentration</td>
<td>Increases drug clearance</td>
</tr>
<tr>
<td>High baseline TNF concentration</td>
<td>May decrease drug concentration by increasing clearance</td>
</tr>
<tr>
<td>High body size</td>
<td>May increase drug clearance</td>
</tr>
<tr>
<td>Sex</td>
<td>Males have higher clearance</td>
</tr>
</tbody>
</table>

Mono vs. Combo with Anti-TNF Therapy: Infliximab
Infliximab Combination Therapy is Superior to Monotherapy in Crohn’s disease

Combo therapy α higher trough levels

Week 46 Median IFX Concentrations

Combination Therapy in Ulcerative Colitis

**Outcomes**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>IFX+AZA (n = 78)</th>
<th>IFX (n = 77)</th>
<th>AZA (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>40%*#</td>
<td>22%</td>
<td>24%</td>
</tr>
<tr>
<td>Response</td>
<td>77%#</td>
<td>69%#</td>
<td>50%</td>
</tr>
<tr>
<td>Mucosal healing</td>
<td>63%#</td>
<td>55%#</td>
<td>37%</td>
</tr>
</tbody>
</table>

*P< 0.05 compared to IFX; #P< 0.05 compared to AZA.

Combination Therapy Benefit Primarily Due to Improved Infliximab (IFX) Levels: SONIC Post-Hoc

Methods
Exposure-response relationships within wk 30 serum IFX concentration (SIC) quartiles +/- concomitant azathioprine (AZA)
206 patients from SONIC

Results
No difference in steroid free clinical remission at week 26 (CSFR26) across quartiles
Non-significant benefit with addition of AZA in mucosal healing (Q1 & Q2)

Benefit of combination therapy primarily due to AZA’s influence on PK of IFX

Addition of IM may Eliminate Anti-drug Antibodies

Patient 1

Patient 2

Patient 3

Patient 4

Start MTX

Start 6-MP

Start AZA

Start AZA

Real Life data: Anti-TNF Monotherapy for Crohn’s: A 13-year Multicentre Experience

Cumulative probability of remaining on anti-TNF therapy was 57.9% at 5 years among the 297 patients not starting an immunomodulator during follow-up

Resetting immunogenicity with an immunomodulator was effective in half of patients

Higher Infliximab Trough Levels Needed for Perianal Fistula Healing

Higher Infliximab (IFX) trough levels are associated with a higher rate of perianal fistula healing and closure

- Cross sectional study of 117 CD patients with active fistulas on IFX for >24 weeks
- Patients with FH had a significantly higher IFX trough levels (using HMSA) than those with active fistulas (18.5 vs. 6.5 µg/mL, P<0.0001)
- Patients with antibodies to IFX had a lower chance of FH
- IFX trough level >10 µg/mL was an independent predictor of FH

Mono vs. Combo with Anti-TNF Therapy: Adalimumab
Clinical remission rate did not differ between the monotherapy and combination groups

Combination therapy was significantly more effective than adalimumab monotherapy in achieving endoscopic response at Week 26 but no difference seen at week 52.

Adverse events were similar in both groups, and trough levels of adalimumab and anti-drug antibodies were similar in the two groups.

SONIC and DIAMOND: How were they different?

- Data on the combination of azathioprine with infliximab and adalimumab showed different findings even with relatively similar study population (SONIC and the DIAMOND)
  - Therapeutic strategies could have different results, even within the same drug class
  - POWER
- Same mechanism of action may not equal similar pharmacokinetic and pharmacodynamic features
- Data from each molecule may not be extrapolatable across anti-TNF agents

Pharmacokinetics of Adalimumab

- **Meta-analysis of ADA** pharmacokinetics of 14 studies
- 1941 patients with mixed IBD diagnoses
- Clinical response associated with higher drug trough and low antibody to ADA
- Combination therapy did not influence antibody or drug trough levels
- Antibodies to ADA appear to cause low trough concentration ADA and lessened clinical effect, **but we lack evidence suggesting that IM have the ability to prevent the development of these antibodies**

REACT: Time to First Hospitalisation, Surgery or Complication

HR (95% CI) = 0.73 (0.62, 0.86), \( p<0.001 \)

CALM: A Prospective, Multicenter, Open-label Randomized Study of Treatment Strategies

Results: Primary Endpoint at 48 Weeks After Randomization

CDEIS <4 and No Deep Ulcerations

<table>
<thead>
<tr>
<th>Clinical Management</th>
<th>Treat to Target</th>
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<tbody>
<tr>
<td>30.3</td>
<td>45.9</td>
</tr>
<tr>
<td>37/122</td>
<td>56/122</td>
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</table>

P = 0.010

Combination Therapy: Evidence for Vedolizumab and IMM?

- **GEMINI 1 and 2**: 30% on Immunomodulator

- Antibodies to vedolizumab (AVA) found infrequently (3.7%-4.1%) of patients at “any time” during testing

- During active VDZ therapy, combination therapy patients had a 3% risk of AVA, compared to 4% for VDZ monotherapy

- Higher levels of anti-drug antibody were seen following completion of VDZ therapy among those patients without IMM compared to those with ongoing IMM use (18% vs. 3%)

- **Benefit of Combination therapy with Vedolizumab and IM unclear**

Combination Therapy: Evidence for Ustekinumab?

• Phase 3 induction and maintenance trials

• 30% of patients received concurrent IMM with Ustekinumab or placebo

• Overall low level of antidrug antibodies at 44 wk of 2.3%

• Data analyzing the effect of combination therapy not yet published

Real Life Retrospective Cohort: Ustekinumab (GETAID)

• Retrospective observational study
• 122 treated patients
• All 122 patients were prior treatment failures with anti-TNF-α inhibitors
• only 18 using IM at the time of ustekinumab therapy
• IM use was found to be a predictor of 3 month clinical benefit, OR = 5.43; 95%CI: 1.14-25.77; \( P=0.03 \)

### Summary of Current Evidence for Combination Therapy in IBD

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<thead>
<tr>
<th></th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Clinical benefit</td>
<td>Pharmacokinetic/immunogenic benefit</td>
</tr>
<tr>
<td>IFX + AZA/6MP (treatment naïve)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IFX + AZA/6MP (step-up from immunomodulator monotherapy)</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>IFX + MTX</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>ADA + IMM</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>VDZ + IMM</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Ustekinumab + IMM</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

IFX: Infliximab; AZA: Azathioprine; 6-MP: 6-mercaptopurine; MTX: Methotrexate; ADA: Adalimumab; VDZ: Vedolizumab; IMM: immunomodulatory; +: beneficial; +/-: Possible benefit; NA: No adequate data available.

COMMIT: Prospective study of Methotrexate with Infliximab

- IFX monotherapy and subcutaneous placebo versus IFX and subcutaneous MTX for patients with CD

- No difference in primary outcome of steroid free remission at week 14 (76% versus 78%)

- MTX can modify immune response to IFX, with lower ATI in the MTX arm vs. placebo, 4% vs. 20% ($P=0.01$), and a trend towards higher IFX trough levels, 6.35 μg/mL vs. 3.75 μg/mL ($P = NS$)

Why not Combination for Everyone?

1. Overtreatment of patients with mild IBD that are unlikely to have progression of disease

2. Susceptible to adverse effects from two drug classes

3. Unlike short term clinical trials, long-term retrospective and prospective series have shown that combination of AZA and anti-TNF is associated with a higher relative risk of opportunistic infection, lymphoma and non-melanoma skin cancer

### Absolute Risk of Hepatosplenic T cell Lymphoma on Immunosuppressive Therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients on thiopurines</td>
<td>1: 45 000</td>
</tr>
<tr>
<td>All patients on thiopurines and anti-TNF</td>
<td>1: 21 945</td>
</tr>
<tr>
<td>Males aged &lt; 35 on thiopurines</td>
<td>1: 7404</td>
</tr>
<tr>
<td>Males aged &lt; 35 on thiopurines and anti-TNF</td>
<td>1: 3534</td>
</tr>
</tbody>
</table>

No Increased Risk of Malignancy in Pediatric Patients Treated with Anti-TNF Monotherapy

- Global, multicenter prospective cohort trial (DEVELOP, n=5,402)
- Comparison with SEER database
- No increased malignancy risk with biologics, including all anti-TNF and non-anti-TNF agents, in the absence of thiopurines
- A 2.7-fold increased risk of malignancy in thiopurine-exposed patients irrespective of biologic exposure

Favorable Long Term Safety of Adalimumab: PYRAMID Registry

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Adalimumab N=5025 n (%)</th>
<th>PYs = 16680.4 Events (E/100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any malignancy</td>
<td>116 (2.3)</td>
<td>134 (0.8)</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>36 (0.7)</td>
<td>49 (0.3)</td>
</tr>
<tr>
<td>Lymphoma (Background rate: 0.084 E/100 PYs, IMM Exposure: 9/10)</td>
<td>10 (0.2)</td>
<td>10 (0.060)</td>
</tr>
</tbody>
</table>

Incidence of Serious Infections

- ADA Monotherapy: 9.6%
- ADA +CS: 11.7%
- ADA +IMM: 12.7% (*p=0.007*)
- ADA +IMM+CS: 12.6% (**p=0.039**)

Incidence of Malignancies

- ADA Monotherapy: 1.9%
- ADA Thiopurines: 3.1%

Summary

• Data obtained for one anti-TNF may not apply to others

• Data are significantly biased by populations included in clinical trials

• Patient selection for treatment based on risk:benefit e.g., combination therapy vs. risks of infections/malignancy: **Not resolved!**
Take Home Messages

• Combination therapy is more effective for Infliximab, especially in those without prior immunomodulator or infliximab use

• Combination may be less important for Adalimumab

• Data lacking for other biologics

• Main mechanism of benefit of combination therapy is likely through favorable effects on immunogenicity/PK

• Consider Combination therapy patients with risk factors for disabling disease, complications or surgery