Is Combination Therapy More Effective for Crohn’s Disease?

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Where did we get the idea that monotherapy with a biologic was the same as combination therapy?
No Difference in Anti-TNF Efficacy in Patients Already Failing Immunomodulator Therapy

Percentage of Patients in remission at week 56

EOW = every other week; IMM = immunomodulator
*P < 0.001; **P < 0.05, adalimumab vs placebo.
Is Combination Therapy More Effective Than Monotherapy?

Yes
Comparison of Treatment Strategies in Early Rheumatoid Arthritis

BeSt Study

Index of bone destruction
Change in SIS

N=508

Time (months)

Sequential monotherapy
Step-up combination therapy with methotrexate
Initial combination with prednisone + methotrexate
Initial combination with infliximab + methotrexate

Response to Adalimumab in Patients With Early vs. Late RA

Mean Changes in Total Sharp Scores

Mean Changes

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo + MTX</th>
<th>Adalimumab 40 mg EOW + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 years</td>
<td>4.7</td>
<td>0.4</td>
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<tr>
<td>&gt; 2 years</td>
<td>2.6</td>
<td>0.1</td>
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EOW = every other week
Clinical Remission Without Corticosteroids at Week 26

Primary Endpoint

- AZA + placebo: 30/170
- IFX + placebo: 45/169
- IFX+ AZA: 57/169

p<0.001
p=0.009
p=0.022

Mucosal Healing at Week 26

- **AZA + placebo**: 16/109 (p<0.001)
- **IFX + placebo**: 30/93 (p=0.023)
- **IFX + AZA**: 44/107 (p=0.055)

Early Combined Immunosuppressive Therapy With Infliximab and Azathioprine Versus Conventional Therapy in Active Early Crohn’s Disease


Newly diagnosed Crohn’s disease (n=129)

Step-up (n=64)

Steroids

+ AZA
+ MTX

+ IFX

Steroids

Top-down (n=65)

IFX (0/2/6) + AZA

IFX + AZA

+ (episodic) IFX

Steroids

The primary endpoints were remission (CDAI <150) and off steroids at months 6 and 12
Early Combined Immunosuppressive Therapy With Infliximab and Azathioprine Versus Conventional Therapy in Active Early Crohn’s Disease

Mucosal Healing

† Endoscopic healing was scored in 5 ileal and colonic segments as follows: 0=no ulcers, 1= aphthoid ulcers, 2=larger ulcers, 3= ulcerated stenosis.
‡ p<.001

Bridge Therapy With Infliximab and Azathioprine as Effective as Both Continuously

![Graph showing comparison between SONIC IFX+AZA and Top Down treatment methods. Series 1 is indicated with blue bars.](image-url)
Bridge Therapy With Infliximab and Azathioprine as Effective as Both Continuously

Steroid Dependence > 6 months

- **Stratum 1 = “AZA failure”**
- **Stratum 2 = “AZA naïve”**

- **Infliximab (Week 0, 2, 6) + AZA/6MP**
- **Placebo (Week 0, 2, 6) + AZA/6MP**

Randomization | Week 24 | Week 52
--- | --- | ---
End-point | Follow-up

Lémann M et al. *Gastroenterology* 2006;130:1054-1061.
Even Immunosuppressor Naïve Patients Benefit From a Biologic

Lémann M et al. *Gastroenterology* 2006;130:1054-1061.

### Percent of Patients in Remission Off Steroids

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<tr>
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<tbody>
<tr>
<td>Week 12</td>
<td>41%</td>
<td>83%</td>
<td>34%</td>
<td>64%</td>
<td>32%</td>
<td>63%</td>
<td>32%</td>
<td>50%</td>
</tr>
<tr>
<td>Week 24</td>
<td>32%</td>
<td>63%</td>
<td>26%</td>
<td>50%</td>
<td>32%</td>
<td>52%</td>
<td>12%</td>
<td>52%</td>
</tr>
<tr>
<td>Week 52</td>
<td>25%</td>
<td>27%</td>
<td>26%</td>
<td>26%</td>
<td>26%</td>
<td>27%</td>
<td>26%</td>
<td>27%</td>
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</tbody>
</table>

- **AZA/6-MP + Placebo**
- **AZA/6-MP + Infliximab 5 mg/kg**
Randomized Placebo-Controlled Trial of Infliximab for Post-op Recurrence of Crohn’s Disease

Endoscopic Recurrence defined as endoscopic scores of i2, i3, or i4.
Combination Therapy Improves Trough Concentrations of the Biologic
Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis.

PK data at Wk 30 was not available for 1 patient treated with AZA + placebo.

3 patients treated with IFX + placebo.

4 patients treated with AZA + IFX.

* IFX and IFX+AZA patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis

SONIC: IFX Trough Levels at Week 30* are Higher With Concomitant AZA

* Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis

COMMIT: Proportion of Patients With Treatment Success is Similar Between Groups


P = 0.83

Week 14

P = 0.86

Week 50

MTX

Placebo

Infliximab plus

% Success

76.2

77.8

55.6

57.1
Proportion of Patients With ATIs is Higher in Patients on Infliximab Monotherapy

Trough Concentration of Infliximab is Higher With Concurrent Methotrexate

Comparative Toxicity of Various Therapies for Crohn’s Disease
Infection and sepsis
- ECCDS, 113 patients received steroids, 2 died of sepsis (1.8%) during the trial and 1 shortly after discontinuing steroids
- NCCDS, 85 patients received steroids, 1 developed sepsis

Abdominal and pelvic abscess
- Retrospective review of 432 patients
- Adjusted odds ratio (OR) for intra-abdominal or pelvic abscess 9.03 (2.40 – 33.98) in patients with perforating CD treated with steroids
- OR 2.81 (0.99-7.99) for abscess in patients receiving prednisolone >20 mg/day
- OR 9.31 (1.03-83.91) for abscess in patients with active disease treated with steroids

Mortality Associated With Current and Recent Corticosteroid Use – Adjusted HR (95% CI)


Current Use of Corticosteroids
- Hazard Ratio: 2.81
- 95% CI: (2.26-3.5)

Recent Use of Corticosteroids
- Hazard Ratio: 2.49
- 95% CI: (1.65-3.75)
Risk of Lymphoma in Patients with IBD Treated With Immunosuppressives (CESAME Study): Study Design

- Cross-sectional, nationwide French CESAME cohort
- 821 gastroenterologists
- 19,486 IBD patients (60% CD, 40% UC or indeterminate IBD)
- 35.3% patients receiving immunosuppressants at baseline
  - Thiopurine (30%)
  - MTX (4%)
  - Anti-TNF (5%)

Incident cases of cancer reported

Expected cases of lymphoproliferative disorders calculated from FRANCIM network

Clinical and histologic characteristics reviewed for validation

### Risk of Lymophoma in Patients With IBD Treated With Immunosuppressives (CESAME Study)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>SIR*</th>
<th>95% CI</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>LPD</td>
<td></td>
<td>1.86</td>
<td>1.08–2.97</td>
<td>0.03</td>
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<tr>
<td>Hodgkin’s disease</td>
<td>1</td>
<td>0.7</td>
<td>0.01–3.92</td>
<td>0.82</td>
</tr>
<tr>
<td>Non-Hodgkin LPD</td>
<td>16</td>
<td>2.07</td>
<td>1.2–3.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Patients naïve to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>immunosuppressives</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients receiving AZA at</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diagnosis</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Deaths in patients with</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>current or previous AZA</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>use</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EBV-associated cases</td>
<td>7†</td>
<td></td>
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*Compared with general population; †Among 11 cases that could be tested for EBV.

AZA, azathioprine; CI, confidence interval; EBV, Epstein-Barr virus; LPD, lymphoproliferative disorders, SIR, standardized incidence ratio

Incidence of LPD According to Thiopurine Exposure


<table>
<thead>
<tr>
<th>Yearly incidence rate (per 1000 patient-years)</th>
<th>Patients-years</th>
<th>Cases of LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td>13595</td>
<td>2325</td>
</tr>
<tr>
<td>50-60 years</td>
<td>7924</td>
<td>1524</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>15732</td>
<td>4965</td>
</tr>
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</table>

Thiopurine therapy
- Continuing
- Discontinued
- Never received
Infections and Mortality in the TREAT Registry: 15,000 Patient-Years of Experience

Multivariate analysis

Mortality

Serious infections

IFX = infliximab; AZA = azathioprine; MTX = methotrexate

Lichenstein GR, et al. *Gastroenterology* 2006;130(suppl 4):A-71
Risk Factors for Opportunistic Infections in IBD: A Case-Control Study

100 cases of opportunistic infections

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
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<tbody>
<tr>
<td>1 medication</td>
<td>2.7 (1.5–4.8)</td>
<td>0.0014</td>
</tr>
<tr>
<td>2 medications</td>
<td>9.7 (3.3–28.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>3 medications</td>
<td>Infinite</td>
<td>Overall P &lt; 0.0001</td>
</tr>
<tr>
<td>Steroids alone</td>
<td>2.2 (1.1–4.8)</td>
<td>0.037</td>
</tr>
<tr>
<td>6-MP/AZA alone</td>
<td>2.5 (1.2–5.1)</td>
<td>0.015</td>
</tr>
<tr>
<td>IFX alone</td>
<td>11.2 (0.8–153.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>6-MP/AZA + steroids</td>
<td>15.7 (4.1–59.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>6-MP/AZA + IFX</td>
<td>1.6 (0.1–18.7)</td>
<td>0.71</td>
</tr>
<tr>
<td>6-MP/AZA + IFX + steroids</td>
<td>Infinite</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

6-MP = 6-mercaptopurine; AZA = azathioprine; IBD = inflammatory bowel disease; IFX = infliximab.
8905 patients representing 20,602 patient-years in 26 anti-TNF trials

13 Non-Hodgkin lymphomas (mean age 52, 62% male)

10/13 exposed to IM*

6/13 died as a result of NHL

<table>
<thead>
<tr>
<th></th>
<th>NHL rate per 10,000</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>SEER all ages</td>
<td>1.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IM alone (Kandiel et al)</td>
<td>3.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-TNF vs. SEER</td>
<td>6.1</td>
<td>3.23</td>
<td>1.5-6.9</td>
</tr>
<tr>
<td>Anti-TNF vs. IM alone</td>
<td>6.1</td>
<td>1.7</td>
<td>0.5-7.1</td>
</tr>
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</table>

* not reported in 2

Conclusions

- Most patients with Crohn’s disease experience a chronic progressive destructive course of disease.
- Combination therapy is more effective than monotherapy esp in immunomodulator naïve patients.
- Steroids have increased risk of serious infection and death.
- Azathioprine and anti-TNF agents have similar risks of opportunistic infection and lymphoma.