Mono vs. combotherapy with Anti-TNFs in CD

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Conflicts of interest

Conseling, boards, transports or fees from Abbvie, Biogaran, Biogen, Ferring, HAC-pharma, Janssen, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda, Theradiag, Tillots.
Combotherapy IFX + AZA vs. monotherapies in CD (SONIC trial)

Colombel JF et al, NEJM 2010

Clinical remission off steroids at w26
(whole population - n=508)

Clinical remission off steroids at w26
(patients with endoscopic lesions - n=325)
Mono/combo: experts’ recommendations

[Diagram showing decision tree for treatment options based on patient characteristics and expert recommendations]

Dulai PS et al, Gut 2014
Mono/combo: experts’ recommendations

Dulai PS et al, Gut 2014
Impact of SONIC on combotherapy with IFX

Canadian retrospective study on IFX use in 673 IBD patients

Elias E et al, 471. DDW 2018
Historical arguments

- Mono
- Combo

Efficacy
Immunogenicity
Safety
Beyond a black & white vision
Many decision criteria

- Type of IBD: CD/fistulating CD/UC
- Type of drug:
  - Anti-TNF agent: IFX/ADA-GLM
  - Conventional IS: thiopurine/MTX
- Prior exposure to IS or mabs
- Treatment phase: induction/maintenance/long-term
- Patient’s characteristics: gender, age, comorbidities
**Comborthrapy IFX + AZA vs. monotherapies in CD (SONIC trial)**

- AZA + placebo
- IFX + placebo
- IFX + AZA

**Clinical remission off steroids at w26**
(whole population - n=508)

- Patients (%): 30.6, 44.4, 56.8

**Clinical remission off steroids at w26**
(patients with endoscopic lesions - n=325)

- Patients (%): 29.6, 50.5, 61.3

P < 0.001
P = 0.009
P = 0.022
P < 0.001
P = 0.002
P = 0.12

Median disease duration: 2.3 years

Colombel JF et al, NEJM 2010
Fistulating ano-perineal CD: predictors of fistula closure

Rennes-Nancy cohort (156 patient treated with IFX), median FU 250 weeks

Median disease duration: 3.8 yrs

Bouguen G et al, CGH 2013
Combotherapy ADA+AZA vs. ADA in CD (DIAMOND trial)

Clinical remission off steroids at w26

- ADA mono: 71.8%
- ADA + AZA: 68.1%

P = 0.63

Endoscopic response at w16

- ADA mono: 63.8%
- ADA + AZA: 84.2%

P = 0.019

Matsumoto T et al, JCC 2016
Combotherapy IFX+MTX vs. IFX mono in CD (COMMIT trial)

Feagan B et al, Gastroenterology 2014
Combotherapy benefits in patients with prior IS failure

Meta-analysis from RCTs

Remission off steroids at 6 months

**Infliximab**

- **OR = 1.79 (1.06-3.01)**

**Adalimumab**

- **OR : 0.93 (0.65-1.34)**

Jones J et al, CGH 2015
Prevention of immunogenicity
Immunogenicity of mabs

<table>
<thead>
<tr>
<th>Biologic agent</th>
<th>All studies (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>0.0–65.3 (73)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0.3–38.0 (22)</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>3.3–25.3 (4)</td>
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<tr>
<td>Vedolizumab</td>
<td>1.0–4.1 (4)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>0.4–2.9 (2)</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>0.7 (1)</td>
</tr>
</tbody>
</table>

Vermeire S et al, Therap Adv Gastroenterol 2018
Immunisation against infliximab

Prospective Israeli cohort (n=125)
Early immunisation against IFX

![Graph showing serum IFX levels over weeks with two groups: ATI negative (n = 13) AUC 1361 mg/L/day and ATI positive (n = 6) AUC 760 mg/L/day.](image)

*P < .01*

Brandse JF et al, CGH 2016
Immunisation against infliximab

Prospective Israeli cohort (n=125)

Ungar B et al, Gut 2014
Anti-TNF immunogenicity according to mono or combo at baseline: the PANTS cohort

Kennedy NA et al., Lancet Gastro 2019
Pharmacologic analysis from the COMMIT trial

### IFX trough levels

<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX μg/mL</td>
<td>6.35</td>
<td>3.75</td>
</tr>
</tbody>
</table>

\[ P = 0.08 \]

### ATI

<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>ATI</td>
<td>4</td>
<td>20</td>
</tr>
</tbody>
</table>

\[ P = 0.01 \]

Feagan B et al, Gastroenterology 2014
Anti-TNF persistence according to mono or combotherapy at baseline (CD)

Cosnes J et al, APT 2016
Combo or mono after immunisation against a first anti-TNF

2nd anti-TNF mono (n=45) vs. combo (n=45)

Survival without anti-TNF failure

Log rank < 0.0001

ADA (réf.)
IFX : HR = 1.29 (0.67-2.53) ; p = 0.46
ADA + AZA : HR = 0.11 (0.02-0.47) ; p = 0.003
IFX + AZA : HR = 0.22 (0.09-0.52) ; p = 0.0007
Risks associated with IS or biologic monotherapy

**Cancer**
- **Thiopurines**: NMSC, lymphoma, urinary tract cancer
- **MTX**: none?
- **Anti-TNF**: melanoma, lymphoma
- **VDZ**: none?
- **USK**: none?

**Opportunistic infections**
- **IS**: CMV, EBV reactivations
- **HPV reactivation?**
- **TB**: Infections with intracellular pathogens
- **HBV reactivation**
- **Intestinal infections (C. diff)**
Risks associated with combotherapy

**Cancer**
- **Thiopurines**: NMSC, lymphoma, urinary tract cancer
- **MTX**: none?
- **Anti-TNF**: melanoma, lymphoma
- **VDZ**: none?
- **USK**: none?

**Opportunistic infections**
- **IS**: CMV, EBV reactivations
- **HPV reactivation?**

**Biologic**
- **TB**: Infections with intracellular pathogens
- **HBV reactivation**
- **Intestinal infections (C. diff)**
## Risk of lymphoma with IBD treatments

Data from the French CPAM (2009-2014)
187 362 IBD (51% CD); median FU: 4.9 yrs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No thiopurine, no anti-TNF</th>
<th>Thiopurine mono</th>
<th>Anti-TNF mono</th>
<th>Combotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>522 487</td>
<td>111 113</td>
<td>60 736</td>
<td>11 514</td>
</tr>
<tr>
<td>Lymphoma (n)</td>
<td>220</td>
<td>70</td>
<td>32</td>
<td>14</td>
</tr>
<tr>
<td>HR adjusted (95%IC)</td>
<td>1</td>
<td>2.60 (1.96-3.44)</td>
<td>2.41 (1.60-3.64)</td>
<td>6.11 (3.46-10.8)</td>
</tr>
</tbody>
</table>

Lemaitre M et al, JAMA 2017
Take-home messages

- Combotherapy improves IFX efficacy (with AZA only)
- Combotherapy improves IFX and ADA pharmacokinetics
- Combotherapy is associated with an increased risk of opportunistic infection and lymphoma
Absence of dedicated trial with vedolizumab or ustekinumab
Benefits of combotherapy with VDZ or USK: retrospective series (patient with prior IS and anti-TNF failures)

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>n IS / N (%)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shelton et al</td>
<td>USA</td>
<td>17/65 (27)</td>
<td>None</td>
</tr>
<tr>
<td>Vivio et al</td>
<td>USA</td>
<td>10/21 (48)</td>
<td>None</td>
</tr>
<tr>
<td>Baumgart et al</td>
<td>Germany</td>
<td>88/115 (77)</td>
<td>None</td>
</tr>
<tr>
<td>Amiot et al</td>
<td>France</td>
<td>26/121 (21)</td>
<td>None</td>
</tr>
<tr>
<td>Kopylov et al</td>
<td>Israel</td>
<td>16/69 (23)</td>
<td>None</td>
</tr>
<tr>
<td>Eriksson et al</td>
<td>Sweden</td>
<td>42/92 (46)</td>
<td>None</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>Kopylov et al</td>
<td>Canada</td>
<td>4/38 (11)</td>
<td>None</td>
</tr>
<tr>
<td>Wils et al</td>
<td>France</td>
<td>18/122 (15)</td>
<td>Positive</td>
</tr>
<tr>
<td>Harris et al</td>
<td>USA</td>
<td>19/45 (65)</td>
<td>None</td>
</tr>
<tr>
<td>Khorrami et al</td>
<td>Spain</td>
<td>42/116 (36)</td>
<td>None</td>
</tr>
<tr>
<td>Ma et al</td>
<td>Canada</td>
<td>73/167 (44)</td>
<td>Negative</td>
</tr>
</tbody>
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