Small molecules and new therapeutic targets

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Do we really need new drugs for IBD patients?
Cumulative probability of thiopurines and antiTNF use – Dutch cohort 1991-2011

Jeuring SFG Am J Gastroenterol 2017
Cumulative hosp & surg rates for Crohn’s disease

Jeuring SFG Am J Gastroenterol 2017
# Future panorama of IBD drugs

## Small molecules

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular weight</strong></td>
<td>Small (&lt;1000 daltons)</td>
</tr>
<tr>
<td><strong>MoA</strong></td>
<td>Receptor or enzyme inhibition</td>
</tr>
<tr>
<td><strong>Location of target</strong></td>
<td>Intracellular</td>
</tr>
<tr>
<td><strong>Target specificity</strong></td>
<td>Less (compared to biologics)</td>
</tr>
<tr>
<td></td>
<td>- Toxicities generally non-specific/not related to target (“off-target toxicity”)</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>Short (compared to antibodies)</td>
</tr>
<tr>
<td></td>
<td>- Minutes – hours - days</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Potential for extensive distribution within the body</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Generally not a concern</td>
</tr>
</tbody>
</table>

## Monoclonal antibodies

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular weight</strong></td>
<td>Large (e.g. mAb = 150 kDa)</td>
</tr>
<tr>
<td><strong>MoA</strong></td>
<td>Depletion</td>
</tr>
<tr>
<td><strong>Location of target</strong></td>
<td>Extracellular</td>
</tr>
<tr>
<td><strong>Target specificity</strong></td>
<td>High target specificity</td>
</tr>
<tr>
<td></td>
<td>- Toxicity generally related to target/pharmacology or “on-target toxicity”</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>Long – especially molecules with Fc or IgG</td>
</tr>
<tr>
<td></td>
<td>- FcRn receptor, protects IgG from catabolism</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>More limited distribution within body</td>
</tr>
<tr>
<td></td>
<td>- Initially, largely confined to vascular space</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Common challenge in animals and humans</td>
</tr>
</tbody>
</table>
Future panorama of IBD drugs

**Biologics**
- Tildrakizumab (MK-3222) / MerckSharp & Dohme Corp
- Guselkumab / Janssen
- Ch5D12 / Tanox
- Basiliximab / Cerimon Pharma
- ADT-974 / AbbVie
- AIN 457 / Novartis
- Laquinimod / Theva
- MDX-1100 / Erybal-Meyers
- Vulsilumab / AbbVie
- MEDI 2070 / Allergan
- PF-00547659 / Shire
- AMG 181 / Amgen

**Small molecules**
- NV52 / Novogen
- CCX 282-B (Verciron) / Chemocentryx
- Amiselimod (MT-1103) / Mitsubishi Tanabe Pharma

**Type:**
- Cytokine blocker
- Anti-Adhesion
- Anti-TNF
- Lymphocytes T
- Other mechanisms

**Phases:**
- Pre-clinic
- Phase 1
- Phase 2
- Phase 3
- Launch

**Drugs:**
- Infliximab / Janssen
- Adalimumab / AbbVie
- Cetuximab / UCB
- Vedolizumab / Takeda
- Ustekinumab / Janssen
- Tofacitinib / Pfizer
**Cell homing**

- **CCR9**
- **α4β7**
- **MadCam1**

**Chemokines**
- **CCL20**

**Tissue damage**

**Epithelial-to-mesenchimal transition**

**Proteases**

**Ulcer**

**Fistula**

**TGF-β**

**βFGF**

**Fibrosis**

**Collagen**

** ECM-producing cells**

**Cytokine-mediated amplification of the inflammatory process**

**T cell accumulation due to defective apoptosis**

- **MadCam1**
- **α4β7**
- **CCR9**
Cell homing

Tissue damage

Epithelial-to-mesenchimal transition

Proteases

TGF-β

bFGF

Collagen

ECM-producing cells

Fibrosis

T helper

Cytokine-mediated amplification of the inflammatory process

T cell accumulation due to defective apoptosis

Ulcer

Fistula

Chemokines

CCL20

T cell homing

MadCam1

CCR9

α4β7

Cell homing
Drugs targeting lymphocyte homing in the gut

Danese S and Panès J, Gastro 2014
Sphingosine-1 Phosphate receptors (S1PR)

- S1PR1: Vascular development and neovascularization, Lymphocyte trafficking, Cell proliferation, Promotes motility and invasion of cancer cells, Inflammation
- S1PR2: Inhibits cell motility, Vascular permeability, S1PR2−/− mice develop B-cell diffuse lymphoma
- S1PR3: Angiogenesis, Transactivates EGF receptor
- S1PR4: Stress fiber formation, Dendritic cell differentiation
- S1PR5: Inhibits migration of esophageal cancer cells, Regulation of oligodendrocyte migration, Migration of natural killer cells
S1PR1 regulate lymphocyte egress from lymph nodes
Ozanimod, a next generation S1PR modulator with selectivity for S1P1R and S1P5R
Ozanimod efficacy in ulcerative colitis

**Phase II**
N= 197

### Week 8
- **Placebo (N=65)**: 6.2%
- **Ozanimod 0.5 mg (N=65)**: 13.8%
- **Ozanimod 1 mg (N=67)**: 16.4%

### Week 32
- **Placebo (N=65)**: 6.2%
- **Ozanimod 0.5 mg (N=65)**: 24.2%
- **Ozanimod 1 mg (N=67)**: 20.9%
# Cardiovascular Safety of Ozanimod

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=65)</th>
<th>Ozanimod, 0.5 mg (N=65)</th>
<th>Ozanimod, 1 mg (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of adverse events</td>
<td>59</td>
<td>45</td>
<td>51</td>
</tr>
<tr>
<td>Adverse event — no. of patients (%)</td>
<td>26 (40)</td>
<td>26 (40)</td>
<td>26 (39)</td>
</tr>
<tr>
<td>Serious adverse event — no. of patients (%)</td>
<td>6 (9)</td>
<td>1 (2)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation of regimen — no. of patients (%)</td>
<td>4 (6)</td>
<td>3 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Adverse cardiac event — no. of patients (%)</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Adverse event occurring in ≥2 patients receiving ozanimod — no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis flare</td>
<td>5 (8)</td>
<td>2 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (6)</td>
<td>3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (5)</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>1 (2)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>0</td>
<td>1 (2)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>0</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Proctalgia</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
</tbody>
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Tran JQ et al. Clin Pharmacol Drug Development 2018
## S1P receptor modulators under study in IBD

<table>
<thead>
<tr>
<th>S1P receptor modulator</th>
<th>Target</th>
<th>Clinical development</th>
<th>Clinicaltrials.gov ID</th>
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</thead>
<tbody>
<tr>
<td><strong>Ozanimod</strong></td>
<td>S1P&lt;sub&gt;1-5&lt;/sub&gt;</td>
<td>Phase III</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02435992</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02531113</td>
</tr>
<tr>
<td><strong>Etrasimod (APD-334)</strong></td>
<td>S1P&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02447302</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02536404</td>
</tr>
<tr>
<td><strong>Amiselimod (MT-1303)</strong></td>
<td>S1P receptor (unknown subtype)</td>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02378688</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02389790</td>
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</table>
Sphingosine-1 Phosphate receptor selectivity

<table>
<thead>
<tr>
<th>pEC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>S1P1</th>
<th>S1P2</th>
<th>S1P3</th>
<th>S1P4</th>
<th>S1P5</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1P</td>
<td>7.1–9.4</td>
<td>8.1–8.5</td>
<td>8.4–9.8</td>
<td>7.2–8.1</td>
<td>7.4–8.9</td>
</tr>
<tr>
<td>Fingolimod-phosphate</td>
<td>8.1–9.5</td>
<td>7.5</td>
<td>7.8–9.4</td>
<td>6.6–9.2</td>
<td>8.2–9.5</td>
</tr>
<tr>
<td>Ozanimod (RPC1063)</td>
<td>9.8</td>
<td>No response&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No response&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No response&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.3</td>
</tr>
<tr>
<td>Etrasimod (APD334)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.10</td>
<td>No response</td>
<td>No response</td>
<td>147</td>
<td>24.4</td>
</tr>
</tbody>
</table>
Etrasimod explorative efficacy in UC

Week 12

3-component MCS Clinical Remission

3-component MCS Clinical Response

Phase II
N= 156

Placebo (N=54)  Etrasimod 1 mg (N=52)  Etrasimod 2 mg (N=50)

Placebo (N=54)  Etrasimod 1 mg (N=52)  Etrasimod 2 mg (N=50)

p<0.001

p=0.028

Sandborn W, UEGW 2018, Vienna
Cell homing

Chemokines

Tissue damage

Epithelial-to-mesenchimal transition

Ulcer

Proteases

Fistula

TGF-β

bFGF

Collagen

ECM-producing cells

Cytokine-mediated amplification of the inflammatory process

T helper

T cell accumulation due to defective apoptosis
Jak inhibitors as a potential therapy for IBD

Monteleone G and Caprioli F. Clin Sci 2010

Fontolizumab

Secukinumab

Tralokinumab
Jak inhibitors as a potential therapy for IBD
Kinase inhibitors as novel therapies

- **Cancer**
  - Transcription, SE-targeting therapies (e.g. CDK7, CDK8, CDK9, CDK12 and CDK13)
  - Receptor tyrosine kinase signalling (e.g. EGFR, KIT, PDGFR, MET and HER2)
  - Proto-oncogenes (e.g. BCR–ABL, mutant PIK3CA and MAPK kinases)
  - Neurodegenerative disease (e.g. LRRK2 and CDK5)

- **Immune system**
  - T cell checkpoint inhibitor synergy (e.g. FAK, EGFR, MEK and CDK4 and/or CDK6)
  - Immune system activation (e.g. TAM kinases, CSF1R and IGF1R)
  - Immunosuppression and vaccine adjuvants (e.g. TAM kinases)

- **Degenerative disease**
  - ER stress (e.g. IRE1α, PERK and Dlk)
  - Angiogenesis (e.g. VEGFR, PDGFR and SRPK1)
Currently available JAK inhibitors
Jak inhibitors as a potential therapy for IBD

- Haematopoiesis Growth
- Th17 differentiation
- Acute phase response
- T cell differentiation
- Lipid metabolism
- Anti-viral immunity
- NK cell activation
- Th1 differentiation
- Macrophage and NK cell activation
- Lymphoid cell maturation and function

EPO, TPO, GM-CSF, GH, IL-3, IL-5
IL-12, IL-23
IL-6
IFNα, IFNβ, IFNγ, IFNκ, IFNλ, IFNA1, IFNA2, IFNA3, IFNA4
IFN-γ
IL-2, IL-4, IL-7, IL-9, IL-15, IL-21

JAK2
JAK2
TYK2
JAK2
JAK1
TYK2
JAK1
JAK2
JAK1
JAK1
JAK3

Tofacitinib
Ruxolitinib
Baricitinib
Peficitinib

Filgotinib
Upadacitinib
Solicitinib
Itacitinib

Decernotinib R333

Non-selective
JAK1-selective
JAK3-selective
Jak inhibitors as a potential therapy for IBD

- Ulcerative Colitis
  - Upadacitinib
  - Tofacitinib
- Crohn's Disease
  - Filgotinib
  - Tofacitinib
- Rheumatoid Arthritis
  - Baricitinib
  - Tofacitinib
- Psoriasis
  - Ruxolitinib
  - Tofacitinib
- Pancreatic Cancer
  - Momelotinib
- Primary Myelofibrosis
  - Pacritinib
  - Ruxolitinib
- Cancer
  - INCB039110
  - INC8039110

Phases:
- Phase 1
- Phase 2
- Phase 3
- Launched
Tofacitinib efficacy in ulcerative colitis

**Phase II**

**CLINICAL RESPONSE**

- Placebo: 42
- 0.5: 32
- 3: 48
- 10: 61
- 15: 78

P = 0.001

**CLINICAL REMISSION**

- Placebo: 10
- 0.5: 13
- 3: 33
- 10: 48
- 15: 41

P < 0.001

Sandborn W, NEJM 2012
Tofacitinib efficacy in ulcerative colitis

Overall Cohort

Induction Cohort

PIII OCTAVE Induction 1
A3921094; NCT01465763

- 10 mg BID N=476
- Placebo N=122

PII Induction
A3921063; NCT00787202

- 10 mg BID N=33
- Placebo N=48

PIII OCTAVE Induction 2
A3921095; NCT01458851

- 10 mg BID N=429
- Placebo N=112

Maintenance Cohort

Nonresponders

PIII OCTAVE Sustain
A3921096; NCT01458574

- 10 mg BID N=196
- 5 mg BID N=198
- Placebo N=198

Re-randomization

Nonresponders

Completers and treatment failures

OCTAVE Open (OLE)
A3921139; NCT01470612

- 10 mg BID N=769
- 5 mg BID N=175
Tofacitinib efficacy in ulcerative colitis

WEEK 8 RESULTS

OCTAVE INDUCTION 1

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Proportion of patients in remission</th>
<th>Placebo</th>
<th>Tofacitinib 10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>8.2</td>
<td>18.5</td>
</tr>
<tr>
<td>Tofacitinib 10 mg BID</td>
<td></td>
<td>P=0.007</td>
<td></td>
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</tbody>
</table>

OCTAVE INDUCTION 2

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Proportion of patients in remission</th>
<th>Placebo</th>
<th>Tofacitinib 10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>3.6</td>
<td>16.6</td>
</tr>
<tr>
<td>Tofacitinib 10 mg BID</td>
<td></td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Sandborn W, NEJM 2017
Tofacitinib efficacy in ulcerative colitis

WEEK 8 RESULTS BY PREVIOUS ANTI-TNF EXPOSURE

OCTAVE INDUCTION 1

OCTAVE INDUCTION 2

Proportion of patients in remission

Prior TNFi exposure

Placebo  Tofacitinib 10 mg BID

Sandborn W, NEJM 2017
Tofacitinib efficacy in ulcerative colitis

MUCOSAL HEALING

OCTAVE INDUCTION 1

Placebo  Tofacitinib 10 mg BID

Patients with mucosal healing

0 5 10 15 20 25 30 35 40 45 50

Treatment group

15.6 31.3

P<0.001

OCTAVE INDUCTION 2

Placebo  Tofacitinib 10 mg BID

Patients with mucosal healing

0 5 10 15 20 25 30 35 40 45 50

Treatment group

11.6 28.4

p<0.001

Sandborn W, NEJM 2017
Tofacitinib efficacy in ulcerative colitis

WEEK 52 RESULTS
OCTAVE SUSTAIN

Placebo 5 mg BID 10 mg BID

Proportion of patients in remission

11.1 34.3 40.6

p<0.001

Sandborn W, NEJM 2017
Tofacitinib efficacy in Crohn’s disease

Panès J, Gut 2017
Tofacitinib efficacy in Crohn’s disease

WEEK 8 RESULTS
CLINICAL REMISSION

Proportion of patients in remission

Placebo 37
5 mg BID 43
10 mg BID 43

Panès J, Gut 2017
Tofacitinib efficacy in Crohn’s disease

WEEK 26 RESULTS
CLINICAL REMISSION

Proportion of patients in remission

Placebo 29
5 mg BID 37
15 mg BID 42

Tofacitinib

Panès J, Gut 2017
Different Tofacitinib efficacy between CD and UC

- Different cytokine milieu between Crohn’s disease and ulcerative colitis

- Role of IL9 and IL22, whose signaling is inhibited by Tofacitinib, in mucosal barrier integrity

- Unknown alterations in microbial ecology of the intestinal mucosa (bacterial, fungal, viral)

Paroni M, unpublished
### Other JAK-inhibitors under study for IBD

<table>
<thead>
<tr>
<th>JAK inhibitor name</th>
<th>Target</th>
<th>Clinical development</th>
<th>Clinicaltrials.gov ID</th>
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</thead>
<tbody>
<tr>
<td><strong>Upadacitinib (ABT-494)</strong></td>
<td>JAK1</td>
<td>Phase III</td>
<td>Phase III NCT03006068, NCT02782663, NCT02819635, NCT02365649</td>
</tr>
<tr>
<td><strong>Filgotinib (GLPG0634)</strong></td>
<td>JAK1</td>
<td>Phase II</td>
<td>Phase III NCT02048618, NCT02914600, NCT02914535, NCT03077412, NCT03046056, NCT02914561, NCT02914522</td>
</tr>
<tr>
<td><strong>PF-06651600</strong></td>
<td>JAK3</td>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td><strong>PF-06700841</strong></td>
<td>JAK1, TYK2</td>
<td>Phase II</td>
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</tr>
</tbody>
</table>
JAK1 inhibitors in Crohn’s disease
Filgotinib efficacy in Crohn’s disease

WEEK 10 RESULTS

Vermeire S, Lancet 2017
Upadacitinib efficacy in Crohn’s disease

Sandborn W, DDW 2017, Chicago IL

### Clinical remission at week 16

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>10,8</td>
</tr>
<tr>
<td>3 mg BID</td>
<td>12,8</td>
</tr>
<tr>
<td>6 mg BID</td>
<td>27</td>
</tr>
<tr>
<td>12 mg BID</td>
<td>11,1</td>
</tr>
<tr>
<td>24 mg BID</td>
<td>22,2</td>
</tr>
<tr>
<td>24 mg QD</td>
<td>14,3</td>
</tr>
</tbody>
</table>

### Clinical response at week 16

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>3 mg BID</td>
</tr>
<tr>
<td>3 mg BID</td>
<td>6 mg BID</td>
</tr>
<tr>
<td>6 mg BID</td>
<td>12 mg BID</td>
</tr>
<tr>
<td>24 mg BID</td>
<td>24 mg QD</td>
</tr>
<tr>
<td>24 mg BID</td>
<td>24 mg QD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior TNFi</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
</tr>
<tr>
<td>≥ 3</td>
<td>14</td>
</tr>
<tr>
<td>Other prior biologics</td>
<td>38</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>27</td>
</tr>
</tbody>
</table>
Upadacitinib efficacy in ulcerative colitis

Phase II-III – U-ACHIEVE

Clinical remission at week 8

Clinical response at week 8

Sandborn W, UEGW 2018, Vienna
## Safety of JAK inhibitors in clinical trials

<table>
<thead>
<tr>
<th></th>
<th>Tofacitinib vs. placebo (OCTAVE Sustain W52)</th>
<th>Filgotinib vs. placebo (FITZROY W20)</th>
<th>Upadacitinib vs. placebo (CELEST W16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>72%-80% vs. 75%</td>
<td>75% vs. 67%</td>
<td>76-84% vs. 73%</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>5%-6% vs. 7%</td>
<td>9% vs. 4%</td>
<td>8%-20% vs. 5%</td>
</tr>
<tr>
<td>AEs leading to</td>
<td>9%-10% vs. 19%</td>
<td>18% vs. 9%</td>
<td>3%-14% vs. 14%</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious infections</td>
<td>0.5%-1% vs. 1%</td>
<td>3% vs. 0%</td>
<td>0%-8% vs. 0%</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>13 patients</td>
<td>1 patient</td>
<td>1 patient</td>
</tr>
<tr>
<td>CV events</td>
<td>2 patients</td>
<td>NA</td>
<td>2 patients</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3 patients</td>
<td>NA</td>
<td>1 patient</td>
</tr>
<tr>
<td>GI perforations</td>
<td>1 patient (OCTAVE induction 1)</td>
<td>NA</td>
<td>2 patients</td>
</tr>
</tbody>
</table>
Tofacitinib: Summary of Adverse Events

- Herpes zoster (up to 5% in higher dose mainenance arm) – twice the rate of anti-TNFs and similar to thiopurines
- Non-melanoma skin cancer increased (SCC and BCC)
- Gastrointestinal performation: risk not increased over placebo
- LDL and HDL cholesterol increase (no cardiovascular impact)
  - Cholesterol levels should be checked 4-8 weeks after starting treatment. Should we treat high LDL with cholesterol lowering meds?
- No immunogenicity with small molecules

Zoster in tofacitinib-treated RA patients: a manageable issue

![Bar chart showing the percentage of patients (in %) who required specific actions in response to zoster. The actions include permanently discontinued, stopped temporarily, no action taken, reduced dose, and unknown. The percentages are 8, 42, 43.1, 0.8, and 6.1, respectively.](image-url)
Changes in LDL are reversible with statin therapy

Apremilast mechanism of action
Apremilast efficacy in ulcerative colitis

N=170

% clinical remission

- Placebo: 13.8%
- Apremilast 30 mg BID: 31.6%
- Apremilast 40 mg BID: 21.8%