Selecting the Right First-line Biologic Agent

William Tremaine, M.D.
Maxine and Jack Zarrow Professor
Mayo Clinic
Rochester, MN, USA

Personalized Medicine

- The right drug
- The right dose
- For the right patient
- At the right time
- Using the right route

Ladak SS et al Pain Management Nurs 2007; 8: 140-5

The Right Treatment

- Pretreatment Genomic Analysis
  - Hepatitis C
  - Cancer
  - TPMT

Gene Expression Profiles Crohn’s Disease

- 37 pt with active CD
  - 19 colitis
  - 18 ileitis
- Top-five gene set
  - TNFAIP6
  - S100A8
  - IL11
  - G0S2
  - S100A9

- Expression profiles prior to and after anti-TNF treatment

Arijs I et al Inflam Bowel Dis 2010; 16; 2090-8

IBD: Response to Treatment Microbiome

<table>
<thead>
<tr>
<th>Biologic /Trial</th>
<th>Bacteria</th>
<th>Relapse Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab STORI Prospective CD Discontinuation Relapse predictors</td>
<td>Faecalibacterium prausnitzii Bacteroides</td>
<td>p=0.014 P=0.030 Independent of CRP p=0.0001</td>
</tr>
<tr>
<td>Vedolizumab CD and UC Perspective</td>
<td>CD: butyrate producers</td>
<td>Lower risk No significant differences</td>
</tr>
</tbody>
</table>

Rajca S et al Inflam Bowel Dis 2014; 20; 978-986
Ananthakrishnan AN et al. Cell Host Microbe 2017;21: 603-10

The Right Biologic

- Infliximab
- Adalimumab
- Certolizumab pegol
- Vedolizumab
- Ustekinumab
- JAK inhibitors
Remission at 52 week Biologics

<table>
<thead>
<tr>
<th>Crohn's Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF 60% x 20% yearly loss of response</td>
<td>Anti-TNF 49%</td>
</tr>
<tr>
<td>Ustekinumab 28%</td>
<td>Tofacitinib 40.6%</td>
</tr>
<tr>
<td>Vedolizumab 25%</td>
<td>Vedolizumab 39%</td>
</tr>
</tbody>
</table>

The Right Patient Circumstances
- Primary Non-responder to Anti-TNF
- Pregnancy
- Lymphoma
- Demyelinating disease
- Cardiac failure

Factors Predictive of a Primary Non-Response to Anti-TNF: Crohn’s
- Disease duration > 2 years
- Small bowel disease
- Smoking
- Normal CrP
- Gene mutations
  - FAS-L (fatty acid synthase ligand)
  - Caspase 9

1° Non-Response to an Anti-TNF and Inferior Response to Next Agent
- Systematic Search
  - Through May 2017
  - 8 RCTs with biologics
  - Stratified for prior exposure to anti-TNF or not
- Estimated relative risks of clinical remission

\[ \Delta \]

Singh S et al J Crohn’s & Colitis January 2018

Vedolizumab 1st Line for UC

Markov Modeling
- Univ. of PENN
- Hypothetical
- 35 y/o man with steroid dependent moderate to severe UC
- 4 models
  1. Vedo prior to IFX plus azathioprine
  2. Vedo after IFX plus azathioprine
- Calculations for 100,000 pt

Scott FI et al Inflam Bowel Diseases Feb 2018; 24: 286-95

The Right Patient Circumstances
- Primary Non-responder to Anti-TNF
- Pregnancy
- Lymphoma
- Demyelinating disease
- Cardiac failure

Outcome at 1 year

<table>
<thead>
<tr>
<th>Remissions</th>
<th>PNR vs #1 ( \Delta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>8981</td>
<td>9981</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>18</td>
</tr>
<tr>
<td>Serious infections</td>
<td>1087</td>
</tr>
</tbody>
</table>

Scott FI et al Inflam Bowel Diseases Feb 2018; 24: 286-95
The Right Biologic Pregnancy

- Infliximab
- Adalimumab
- Certolizumab pegol
- Vedolizumab
- Ustekinumab

Optimal Anti-TNF Stop Week During Pregnancy Depends on Anti-TNF Type

- Prospective
- Single center
- 320 live births
  * 131 Anti-TNF
  * 73 Infliximab
  * 58 Adalimumab
- CD 82%, UC 17%, IBDU 1%
- Anti-TNF stopped at various times before delivery
- Cord blood samples measured for Anti-TNF

Kanis SL et al. Rotterdam DDW 2017 Oral # 332c

Optimal Anti-TNF Stop Week During Pregnancy Depends on Anti-TNF Type

- IFX 22-24 wk
- ADA 33-36 wk

The Right Biologic Pregnancy: Certolizumab

- 16 women with CD
- Certulizumab pegol throughout pregnancy
- Maternal / infant blood levels
  * 14 infants per protocol
- Conclusion: Minimal placental transfer

Mariette X et al Ann Rheum Dis 2018; 77:228-33

The Right Patient Circumstances

- Primary Non-responder to Anti-TNF
- Pregnancy
- Lymphoma
- Demyelinating disease
- Cardiac failure

Data from clinical trials and post-marketing reports CD & UC

<table>
<thead>
<tr>
<th>Vedolizumab Treatment</th>
<th>Ustekinumab Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers 27</td>
<td>No safety concerns</td>
</tr>
<tr>
<td>Fathers 19</td>
<td>No safety concerns</td>
</tr>
</tbody>
</table>

Mahadevan U et al Alim Phar Ther 2017; 45: 941-50
Contes X et al J Clin Pharm Ther 2017; 42: 234-6
The Right Biologic
Anti-TNF & Lymphoma Risk

- Micromedex: "increased risk"

Rheumatoid Arthritis Patients in the UK

<table>
<thead>
<tr>
<th>Number who developed Lymphoma</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF 11,931</td>
<td>1.0</td>
</tr>
<tr>
<td>No Anti-TNF 3,367</td>
<td>30</td>
</tr>
</tbody>
</table>

Conclusion: No increased risk

Mercer LK et al Ann Rheum Dis 2017;76:497-503

The Right Biologic
Anti-TNF and Demyelinating Disease

- Micromedex: "New or worsening demyelinating disorders (eg, multiple sclerosis, optic neuritis, peripheral demyelinating disorders including Guillain-Barre syndrome) have rarely been reported"
- Anti-TNF therapy for MS in 2 clinical trials showed worsening
- Many case reports of CNS and peripheral demyelinating disease after anti-TNF therapy
- But, prospective trials and post-marketing registries have not shown a risk

Kemanetzoglou E et al Curr Neurol Neurosci Rep 2017; 17:36

The Right Biologic
Anti-TNF & Heart Failure

- Controversial
- Micromedex: "Use should generally be avoided in patients with heart failure; monitor and discontinue if new or worsening symptoms develop"

<table>
<thead>
<tr>
<th>150pt Heart Failure NYCHA Class III or IV Death or Hospitalization up to 28 wk</th>
<th>IFX 5 mg/kg</th>
<th>IFX 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>IFX 5 mg/kg</td>
<td>13</td>
<td>p=0.043</td>
</tr>
<tr>
<td>IFX 10 mg/kg</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Chung ES et al Circulation 2003;107: 3133-40

The Right Biologic
Special Circumstances

- Primary Non-responder to Anti-TNF
- Pregnancy
- Lymphoma
- Demyelinating disease
- Cardiac failure

The Right Biologic

- Infliximab
- Adalimumab
- Certolizumab pegol
- Vedolizumab
- Ustekinumab
- JAK inhibitors
Janus Kinase (JAK) Inhibition

- JAK phosphorylate activated cytokine receptors
  - Recruit STAT transcription
- Inhibitors block
  - IL-2, IL-4, IL-15, IL-21,
  - T_h2 cell differentiation
  - IFN-γ, IL-6
  - T_h1 cell differentiation

Efficacy and Safety of Oral Tofacitinib as Maintenance Therapy for Moderate to Severe UC: OCTAVE Sustain Trial

- 593 UC patients
- Clinical response with induction phase
- Randomized to:
  - Placebo     198
  - Tofa 5 mg BID       198
  - Tofa 10 mg BID       197
- 52 weeks
- 1 endpoint: remission
  - Mayo Score ≤2
  - Bleeding score 0
  - No subscore >1

Sandborn WJ et al UCSD LaJolla CA, USA oral #1080

Tofacitinib Crohn’s Disease

- 2 Randomized, double-blind, placebo-controlled, multicenter, 2 dose trials.
- 460 patients
- No statistical differences compared to placebo


Efficacy and Safety of Oral Tofacitinib as Maintenance Therapy for Moderate to Severe UC: OCTAVE Sustain Trial

- 593 UC patients
- Clinical response with induction phase
- Randomized to:
  - Placebo     198
  - Tofa 5 mg BID       198
  - Tofa 10 mg BID       197
- 52 weeks
- 1 endpoint: remission
  - Mayo Score ≤2
  - Bleeding score 0
  - No subscore >1

Sandborn WJ et al UCSD LaJolla DDW 2017 oral #1080

Janus Kinase (JAK) Inhibition

- JAK phosphorylate activated cytokine receptors
  - Recruit STAT transcription
- Inhibitors block
  - IL-2, IL-4, IL-15, IL-21,
  - T_h2 cell differentiation
  - IFN-γ, IL-6
  - T_h1 cell differentiation
Filgotinib & Crohn’s Disease

- Selective JAK1 inhibitor
- 52 centers in Europe
- 174 pt, mod-severe disease
- Randomized
  - Filgotinib 200mg p.o.
  - Placebo
- Primary Outcome
  - Clinical remission at 10 weeks

Vermeire S et al Lancet 2017; Jan 21: 266-75

Filgotinib Fistulizing Crohn’s Disease

- Phase 2, Randomized, Placebo-controlled
- April 2017-May 2019
- 75 patients

ClinicalTrials.gov NCT03077412

Personalized Medicine

- The right drug
- The right dose
- For the right patient
- At the right time
- Using the right route

Ladak SS et al Pain Management Nurs 2007; 8: 140-5

The Right Dose
Therapeutic Drug Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Minimum Therapeutic Trough Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>3 μg/ml</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>5 μg/ml</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>15 μg/ml</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>0-8-1.4 μg/ml</td>
</tr>
</tbody>
</table>

The Right Patient
High Risk Crohn’s Disease

- Young age at disease onset
- Fistulizing / stricturing disease
  - Fistula at 1st presentation
- Perianal disease
- Cigarette smoking
- Foregut disease
- Early post-operative recurrence

Personalized Medicine

• The right drug
• The right dose
• For the right patient
• At the right time
• Using the right route

Ladak SS et al Pain Management Nurs 2007; 8: 140-5

At the Right Time

• Prior to:
  • growth impairment
  • fixed strictures
  • loss of continence

The Right Route

• Dependability of the patient
• Practicality of i.v. infusions
  • Expense
  • Distance to an infusion center

The Right Biologic

Conclusions

• None of the current biologics are superior for every patient with IBD
• Criteria to select the optimal biologic for a patient are not yet well-defined
• The clinician’s choice of a biologic for a specific should take into account:
  • Past treatments
  • Pregnancy
  • Co-morbidities
  • Patient compliance