NEW THERAPEUTIC OPTIONS FOR THE MANAGEMENT OF IBD

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Disclaimer

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Learning Objectives

- To summarize our multidisciplinary therapeutic goals and outcomes with the available agents in patients with IBD

- To describe evidence on the efficacy, limitations, safety of available agents and summarize active research with promising new agents
THERAPEUTIC GOALS IN IBD

- Clinical improvement
- Clinical remission
- Corticosteroid weaning
- Maintenance of remission
- Maintained mucosa & transmural healing
- Decrease in hospitalization & surgical interventions
- Prevention of complications
- Change natural course of the disease
HISTORY OF IBD TREATMENT

1979 → Sulfasalazine, steroids
1980 → Antibiotics, Azathioprine, 6-MP
1993 → 5-ASA
1994 → Budesonide
1995 → Mtx
1998 → Infliximab
2007 → Second generation anti-TNF agents
2014 → New agents
2015 → Biosimilars
BIOLOGIC AGENTS in 2018

- **Anti-TNF Agents:**
  - Infliximab [Remicade]
  - Adalimumab [Humira]
  - Certolizumab [Cimzia]
  - Golimumab [Simponi]

- **Integrin Inhibitor Agents:**
  - Natalizumab [Tysabri]
  - Vedolizumab [Entyvio]

- **Anti-IL-12/23 Agents:**
  - Ustekinumab [Stelara]

- **Biosimilars**
## SONIC STUDY

### OUTCOME

<table>
<thead>
<tr>
<th>outcome</th>
<th>AZA alone</th>
<th>INF alone</th>
<th>AZA/INF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid free remission [%]</td>
<td>30.6</td>
<td>44.4</td>
<td>56.8</td>
</tr>
<tr>
<td>Mucosal healing [%]</td>
<td>16.5</td>
<td>30.1</td>
<td>43.9</td>
</tr>
</tbody>
</table>

NEJM 362: 1383, 2010
The focus of the BT will be changing the natural history of CD for a long-standing deep remission.

Earlier intervention is better & the top-down tx may be the future direction in the selected patients with close monitoring.

Trough levels of anti-TNFs correlate by healing.

The maintenance therapy should be arranged following the successful induction.

Aliment Pharmacol Ther 33:857, 2011
Recent outcome of Anti-TNFs in CD

- Anti-TNFs induce 30% CRm & 50% CRs in pts with CD. The secondary loss of response may vary between 10 to 50% depending on the maintenance tx years.

- The BT with anti-TNFs is effective;
  - Remission response: 50 & 80%
  - Steroid discontinuation: 50 & 70%
  - Healing of active fistulas: 30%
  - Decrease complications, hospitalization & surgical interventions

- Anti-TNFs were well tolerated with a good safety profile.
Vedolizumab: A Humanized, Monoclonal Antibody (mAb) Against $\alpha 4\beta 7$ Integrins

- Targets only $\alpha 4\beta 7$ integrin
- Created by insertion of ACT-1 CDRs into human IgG1 framework
- Two amino acid substitutions abrogate Fc-receptor binding and complement fixation (ADCC)
- IV infusion over 30 – 60 minutes
VEDOLIZUMAB [Entyvio]

- Humanized GI-selective MCA against alfa4beta7 integrin that blocks gut lymphocyte trafficking.

- The CRm was 14.5% vs. 6.8% with placebo at 6 wks [1]. In other study, the CRm 39% vs. 21.6% with placebo [2] & recently, a 12 months rates of CRm and mucosal healing were 35% & 63% respectively with 6% AEs [3].

- No PML or serious AEs were seen.

1] NEJM 369: 711, 2013
2] ECCON oral presentation 13, 2013
**Ustekinumab Background**

- Ustekinumab is a fully human IgG1k monoclonal antibody
- Binds the p40 subunit of human IL-12/23
- Prevents IL-12 and IL-23 from binding IL-12Rβ1; mediated signaling and cytokine production
- Approved for psoriasis & CD by the FDA
USTEKINUMAB [Stelara]

- 336 pts with refractory CD responded with 49% CRm vs. 27% of pts on placebo at wk 22 in phase II studies [1].
- The approved doses are weight-based IV infusion for induction & then, maintenance with 90 mg SC q 8 weeks.
- Open label studies showed up to 74% CRm and 89% continued to maintain CRs at 12 months [2].
- No deaths or serious AEs were reported [1-3].

1. NEJM 367: 1519, 2012
New Agents in Development for the Treatment of CD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etrolizumab</td>
<td>Anti-beta-7</td>
<td>GI spec. integrin antagonist</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Anti-IL-6</td>
<td>Humanized MCA</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>Anti-IL-17</td>
<td>Humanized MCA</td>
</tr>
<tr>
<td>Risankizumab</td>
<td>Anti-IL-23</td>
<td>Humanized MCA</td>
</tr>
<tr>
<td><strong>Tofacitinib</strong></td>
<td>Anti-JAK 1-3</td>
<td>Immunomodulator</td>
</tr>
<tr>
<td><strong>Filgotinib</strong></td>
<td>Anti-JAK 1</td>
<td>Immunomodulator</td>
</tr>
<tr>
<td>Ozanimod</td>
<td>Sphingosine1P1R</td>
<td>Lymph. receptor agonist</td>
</tr>
<tr>
<td><strong>AJM300</strong></td>
<td>Anti-alfa-4</td>
<td>Integrin antagonist</td>
</tr>
<tr>
<td>PPC</td>
<td>GI mucus</td>
<td>Phosphatidylcholine</td>
</tr>
<tr>
<td>Mongerson</td>
<td>Smad-7 inhibitor</td>
<td>Antisense oligonucleotide</td>
</tr>
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*PO agents

Modified from Ertan & Stewart: JGPHR 2: 2, 2017
Therapeutic Targets for Lymphocyte Trafficking

Leucocyte Adhesion

LEUCOCYTE

CD 11a/CD18
NATALIZUMAB

CCX282-B
CCR9

ISIS-2302

CCL-25

ICAM-1

ACTIVATED INTESTINAL MICROVASCULAR ENDOTHELIAL CELLS

MAdCAM mAb (PF-547659)

MAdCAM-1

VCAM-1

VEDOLIZUMAB

α4β7

ETROLIZUMAB

Adapted from Danese S Gut 2011;60:998-1008
ORAL TOFACITINIB [Xeljanz]

- This oral immunomodulator inhibits JAK -1,-3 & > -2; modulates cytokines IL-2, 4, 7, 9, 15, & -21.

- The initial studies in pts with CUC showed significant effectiveness 41 to 48% vs 10% (10 to 15 mg BID vs placebo) at wk 8, but pts with CD did not respond well.

- AEs are opportunistic infections, anemia, neutropenia, lymphopenia, hyperlipidemia, transient transaminase & creatinine elevation. Teratogenic in rats & rabbits.

NEJM 367:616-24, 2012
AJG 3: 38-44, 2016
Filgotinib modulates IL-6,11,12,23,27 &-35.

The phase-II study in 174 pts with refractory CD showed CRm 47% with Filgotinib tab. vs 23% with placebo at the end of 20th week.

The safety profile was acceptable. Similar as Tofacitinib, serious AEs were 9% with Filgotinib- > serum LPs, neutropenia, testicular toxicity?!- and 4% with placebo.

Oral sphingosine-1-phosphate receptor, Ozanimod

- Ozanimob, RPC1063 is an anti-trafficking modulator to reducing infiltration of lymphocytes
- A phase II study in CUC showed CRm 57% with 1 mg/d Ozanimod & 37% with placebo at wk 8
- Significant MHRs demonstrated with Ozanimod compared with pl. [33% vs 12%] at wk 32
- AEs were similar to placebo

JCC 9: S15, 2015
Oral AJM 300- alfa-4 integrin ab

- A RCS of 71 pts with CD showed mild reduction in CDAI & CRP compared with placebo [1]
- A phase II study with 102 CUC reported significant CRs (62.7 vs 23.5%) & MHR rates (25.5 vs 3.9%) compared to placebo [2] in 8 wks
- No serious AEs or PML have been reported [1-2]

Oral GI mucus-phosphatidycholine (PPC)

- PCP can strengthen the integrity of the GI defense system and prevents antigenic interactions
- A RCS with steroid-refractory CUC pts showed CRs 50% with PCPP & 10% with placebo plus significant MHRs & improvement in QoL. Similar results are seen in CUC patients with mesalamine –refractory(1).
- The only AE of original formula, bloating, was not seen with modified-release formulation(2).

JCG 44: 101-7, 2010
AJG 109: 1041-51, 2014
Oral MONGERSEN, Antisense Oligonucleotide

- Inhibits T-cell proliferation by inactivating SMAD7, binds TGF-beta-1 & reduces cytokines
- A Phase II study with refractory CD showed 62-67% CRm with Mongersen tab. 40-160 mg/d vs. 10% CRm with pl. at day 14 & maintained at day 28
- Its AEs were similar to placebo but long-term fibrosis issue & others!!!

NEJM 372:1104-13, 2015
AJG 3: 38-44, 2016
BIOSIMILARs [BSs]

- 22 BSs have been used in EU since 2005 & 71 other countries. BSs has been produced to close resemble a drug whose patent has expired. Inflectra [by Celltrion] as Infliximab BS and Amjevita [by Amgen] as Adalimumab BS in 2016 are approved by the FDA.

- The Biologic Price Competition & Innovation Act was passed as a part of ACA in 2010. The Supreme Court ruled to speed BSs to market, eliminating ‘the patent dance’ in June 2017.

Curr Opin Gastroenterol 31: 290, 2015
Gastroenterol & Hepatol 12: 119, 2016
Cl Gastroenterol Hepatol 14; 1685, 2016
CAUTIONS for BIOSIMILARS [BSs]

- Biologics are made in living organisms with a huge complexity. BSs are manufactured with the same amino acid sequence as the reference anti-TNFs.

- “High similarity” does not mean “similar clinical results”. The interchangeability is uncertain for BSs with the reference anti-TNFs.

Arthritis Res Ther 18; 25 & 82, 2016
Cl Gastroenterol Hepatol 14; 1685, 2016
BSs - Facts of Extrapolation

- BSs are ‘highly similar’ but not the identical. Postmarketing studies may be needed to settle the controversy of extrapolation.
- While it could reduce costs [40%?], but no solid data available to confirm the PK/PD profiles, efficacy, safety, switch data, an immunogenicity with these blockbusters[!] in pts with IBD.
- The BSs is supported by most insurance comps in the EU, not yet in the US [econosimilars!!].

Scand J Gastroenterol 51:22, 2016
Cl Gastroenterol Hepatol 14; 1685, 2016