Tumor Necrosis Factor Inhibitors and Treatment In Autoimmune Disease

Ivan J. Fuss, MD

IBD in the United States

• Incidence: 10 cases per 100,000 per year
  ▪ Onset: 30% between 10 and 19 years
  ▪ Young children: 2%

• Prevalence: 100 cases per 100,000
  ▪ More than 1 million cases estimated in United States
  ▪ Ulcerative colitis: 50%
  ▪ Crohn’s disease: 50%

Global Prevalence of IBD

Etiologic Hypotheses

Persistent infection
- Mycobacteria
- Helicobacter sp.
- Measles-mumps
- Listeria
- Toxigenic E. coli

Defective mucosal integrity
- Altered mucus
- Increased permeability
- Cellular starvation
- Impaired restitution

Dysbiosis
- ↓ protective bacteria
- ↑ aggressive commensals

Dysregulated immune response
- Loss of tolerance
- Aggressive cellular activation
- Defective apoptosis
The chronic inflammation of IBD is due to a dysregulated immune response to antigens in the intestine.

- Innate and adaptive immune system
- Epithelial barrier function
- Composition of microbial flora
- Genetic and environmental exposures
- Defects in regulatory mechanisms

Crohn's Disease: Anatomic Distribution

- Small bowel alone (33%)
- Ileocolic (45%)
- Colon alone (20%)
Disease Distribution at Presentation: UC

n=1116

37%
46%
17%


Ulcerative Colitis: Endoscopy
Crohn’s Disease: Endoscopy

Serpiginous ulcer, a classic finding in Crohn's disease
Histology

**Ulcerative Colitis**
- Inflammation limited to mucosa and submucosa
- Submucosa often compressed
- Crypt abscesses common
- Goblet cells diminished
- Epithelioid granulomas absent in submucosa and deeper tissue levels

**Crohn’s Disease**
- Transmural inflammation with lymphoid aggregates
- Submucosa expanded by inflammation and fibrosis
- Crypt abscesses less common
- Goblet cells often normal
- Granulomas are frequent (40-60%)

**CD - Distinguishing Features**
- Strictures
- Endoscopic features
  - Granuloma
  - Focal lesions
  - Asymmetric involvement
  - Fistulization
  - Skip lesions
  - Small bowel involvement
- Rectal sparing
- Perineal disease
- 20-30% without gross bleeding
Crohn’s Disease
Ileocolitis
Transmural
Granulomas

Ulcerative Colitis
Colitis
Superficial
Crypt Abscesses/Ulceration

T Cell Differentiation

Fuss et al IBD 2006
Innate and Adaptive Immune Responses

Adhesion and Recruitment
Mucosal and Inflammatory Zip Codes

- VCAM-1
- MAdCAM-1
- Chemokines
- Leukocyte
- Vascular Endothelium
- Antigen
- DC
- T
- IL-12/18
- IL-10
- TGF-β
- Treg
- MAC
- TNF-α
- IFN-γ
- IL-1β
- IL-6
Immunological Factors in IBD: Crohn’s Disease
Key Inflammatory Mediators in Crohn’s Disease


Crohn’s Disease Requires a “Double Hit”

1. TLR/NLR Signals
2. Microbiota Antigens
Crohn’s Disease Results from a Dysregulated Response to Mucosal Ligands and Antigens

Immunological Factors in IBD: Ulcerative Colitis
TRUC Model

Garrett et al Cell 2007

TRUC Model-II

Garrett et al Cell Host Microbe 2010
**Histopathologic Features of Oxazolone Colitis**

- Pancolitis
- Superficial Inflammation
- Epithelial Cell Loss/Ulceration
- Poly and mononuclear infiltration
- Mucin Depletion

Boirivant and Fuss et al 1998

**NKT Cells and IL-13 in Ulcerative Colitis**

Heller et al Gastroenterology 2005  
Fuss et al J Clin Invest 2004
Depletion of LPMC CD161+ T cells in UC leads to decreased IL-13 production

Fuss et al. J Clin Invest 2004

IL-13 and IFN-γ Secretion by IBD LPMCs

IL-13 secretion (pg/ml)

IFN-γ secretion (pg/ml)

Control

Crohn's Disease

Ulcerative Colitis

0

1000

2000

3000

4000

5000

6000

7000

8000

9000

10000

11000

12000

13000

14000

0

200

400

600

800

1000

1200

1400

0

1000

2000

3000

4000

5000

6000

7000

8000

9000

0

100

200

300

400

500

600

700

800

900

0

100

200

300

400

500

600

700

800

900

LPMC

CD161 depleted LPMC
IL-13 Enhances Cytotoxicity of NKT Cells

- Invariant NK T cell line
- Ulcerative Colitis NK T Cells

Crohn’s Disease
- Ileocolitis
- Transmural Granulomas
- Th1/Th17 Inflammation: IL-12/IL-23, IFN-γ, IL-17, TNF-α

Ulcerative Colitis
- Colitis
- Superficial Crypt Abscesses/Ulceration
- Th2-like Inflammation: IL-13, IL-5, TNF-α

Fuss et al IBD 2006
Gut Lumen

Glycolipid antigen or Ag (i.e. Oxazolone)

Epithelium

APC

NKT

CD1

Glycolipid

Biologic Treatment

Strategies in CD

Biologic Treatment

Strategies in CD
### Treatment of Colitis by Inhibition of Th$_1$

<table>
<thead>
<tr>
<th>Colitis</th>
<th>Treatment</th>
<th>Attenuated/ No Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF$\alpha$</td>
<td>Anti-IFN$\gamma$</td>
<td>Anti-IL-12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Th$_1$</td>
</tr>
</tbody>
</table>

### Generations of TNF-\(\alpha\) Antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Mouse Protein</th>
<th>Human Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afelimomab</td>
<td>100% Mouse Protein</td>
<td>0% Human Protein</td>
</tr>
<tr>
<td>Infliximab</td>
<td>25% Mouse Protein</td>
<td>75% Human Protein</td>
</tr>
<tr>
<td>Adalimumab “D2E7”</td>
<td>0% Mouse Protein</td>
<td>100% Human Protein</td>
</tr>
<tr>
<td>Fully Human</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Construct of Anti-TNF-α Biologic Agents**

**Infliximab**
- Chimeric monoclonal antibody (75% human IgG1 isotype)
- Mouse Human
- PEG, polyethylene glycol.

**Adalimumab**
- Human recombinant antibody (100% human IgG1 isotype)

**Certolizumab Pegol**
- Humanized Fab’ fragment (95% human IgG1 isotype)

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**Infliximab-Treated Patients with Crohn’s Disease**

Clinical response defined as a ≥ 70-point decrease in CDAI score from baseline.
Clinical remission defined as a CDAI score < 150.

- Placebo (n=25)
- Infliximab 5, 10, and 20 mg/kg (n=83)

Maintenance of Remission in CD: Different Studies, Similar Efficacy

<table>
<thead>
<tr>
<th>Week 26–30</th>
<th>Infliximab 5 mg/kg</th>
<th>Adalimumab 40 mg EOW</th>
<th>Certolizumab 400 mg 4-weekly</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction (≥70 pts and ≥25% in CDAI)</td>
<td>51</td>
<td>52</td>
<td>63</td>
<td>27</td>
</tr>
<tr>
<td>Response (Δ100)</td>
<td>27</td>
<td>26</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>Remission (CDAI&lt;150)</td>
<td>39</td>
<td>40</td>
<td>48</td>
<td>40</td>
</tr>
</tbody>
</table>

Biologic Treatment Strategies in UC
ACT1 and ACT2: Results at Week 8

Clinical response

<table>
<thead>
<tr>
<th>Placebo</th>
<th>5 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.3</td>
<td>44.1</td>
<td>49.2</td>
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</tbody>
</table>

Clinical remission

<table>
<thead>
<tr>
<th>Placebo</th>
<th>5 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.9</td>
<td>33.9</td>
<td>27.4</td>
</tr>
</tbody>
</table>

Rutgeerts P et al. DDW 2005, # 689; Sandborn W et al. ibid, # 688
Comparison of anti-Th1 biologics

% Patients in remission

- Placebo
- Etanercept
- Infliximab
- Adalimumab
- Fontolizumab
- Anti-IL-12

- Sandborn W et al Gastro 2001:121
- Infliximab based on Rutgeerts et al. Gastro 2004:126
- Adalimumab 160, 80mg dose
- Hommes et al. Fonto 4mg/kg at 28d
- Mannon et al. AGA 2004

Infliximab: Mechanism of Action

- Membrane-bound TNFα
- Activation of complement (in vitro)
- Infliximab
- Soluble TNFα
- TNFα
- Target cell
- Macrophage

- TNF receptor
Crohn’s disease patients have a decreased ability to undergo apoptosis. Boirivant et al. Gastroenterology 1999

Infliximab induces Apoptosis of Crohn’s disease patients monocyte population

Extrinsic pathway:
- DNA damage
- Cellular stress
- Deprivation of growth factors

Intrinsic pathway:
- Bid
- Fas
- Fas Ligand
- FADD
- Pro-caspase-8
- Bcl-2
- Bcl-xl
- Bax, Bak

Caspase-3

APOPTOSIS

Siegel Figure 2

Lugering et al. Gastroenterology 2001
Decreased cell death may be due to overexpression of anti-apoptotic protein Bcl-2

Infliximab induces changes in the Bax/Bcl-2 pathways
Increased active Caspase-3 expression is observed after Infliximab administration

Infliximab but not Etanercept can induce Apoptosis of Lamina Propria T cells

Van den Brande et al. Gastroenterology 2003
Figure 2. Effects of TNF blockade on antigen-induced production of IFNγ in whole blood cultures stimulated with M. tuberculosis culture filtrate.

Wallis et al 2007
Infliximab: Mechanism of Action

Figure 4. Effect of TNF blockade on apoptosis in 48-hour cultures of M. tuberculosis culture filtrate-stimulated monocytes. Symbols indicate:

- **Infliximab**
- **Adalimumab**
- **Etanercept**

Wallis et al 2007
Side-effects of anti-TNF agents

- Hypersensitivity reactions
  - infusion or injection site reactions
  - serum sickness/delayed hypersensitivity
- Immunogenicity
- Headache
- Rash

- Infections
  - mild and serious
- Demyelinating disorders
- Autoantibodies
- Pancytopenia
- Heart failure
- Hepatotoxicity
- Malignancy

Are serious infections more common if taking more than 1 medication?

- TREAT registry
  - Corticosteroids (HR 2.0, 95% CI 1.4-2.9)
  - Narcotics (HR 2.7, 95% CI 1.9-4.0)

- Opportunistic infections

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
</tr>
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<tr>
<td>1 medication</td>
<td>2.9 (1.5-5.3)</td>
</tr>
<tr>
<td>2 or 3 medications</td>
<td>14.5 (4.9-43)</td>
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</table>
Infliximab Surveillance: Opportunistic Infections

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Reports per 1000 Pt-Yrs*</th>
</tr>
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<tbody>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>0.07</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>0.05</td>
</tr>
<tr>
<td>Listeriosis</td>
<td>0.06</td>
</tr>
<tr>
<td>Atypical mycobacteria</td>
<td>0.05</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>0.04</td>
</tr>
<tr>
<td>CMV infections</td>
<td>0.04</td>
</tr>
<tr>
<td>Legionella</td>
<td>0.03</td>
</tr>
<tr>
<td>Systemic candidiasis</td>
<td>0.03</td>
</tr>
<tr>
<td>Salmonella</td>
<td>0.03</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>0.02</td>
</tr>
</tbody>
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*Risk of death from sepsis = 4/1000 pt-yrs*

*Since first exposure Data on file, Centocor, Inc.*
Who are the patients who are dying from sepsis related to anti-TNF?

- Older
  - Average age = 63 (systematic review); 67 (Mayo)
- Multiple co-morbidities
- Concomitant steroids and/or narcotics
- Long-standing disease

Young “healthy” patients are not in the clear, but probably less at risk

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Risk of NH Lymphoma with anti-TNF treatment for Crohn’s Disease

Meta-analysis Results

- 8905 patients representing 20,602 pt-years of exposure
- 13 Non-Hodgkin lymphomas \( \Rightarrow 6.1 \text{ per 10,000 pt-years} \)
- Mean age 52, 62% male
- 10/13 exposed to IM* (so this is really a study of combo Rx)

<table>
<thead>
<tr>
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<th>NHL rate per 10,000</th>
<th>SIR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>SEER all ages</td>
<td>1.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IM alone</td>
<td>3.6</td>
<td>-</td>
<td>-</td>
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<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>
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</table>

Sircic et al., Gastro 2008;134(4) A14
*not reported in 2
Hepatosplenic T-cell lymphoma

- 9 cases in IBD with 6MP/AZA alone
- 16 cases in IBD patients taking infliximab or adalimumab with 6MP/AZA
  - Age range 12-58 years old
  - Average age = 23 years old
  - Almost all are male (15/16)
  - Infusions ranged from 1-24
  - 7 patients had ≤ 3 infusions
  - Three received adalimumab (after infliximab)
  - Appears to be universally fatal

HSTCL – How big of a problem is this?

- Over 1 Million anti-TNF treated patients worldwide
- About 4.5 Million patient-years of exposure
- No anti-TNF monotherapy (but not many out there)
### PID & Genetic Susceptibility to Infections

<table>
<thead>
<tr>
<th></th>
<th>Bacterial</th>
<th>Viral</th>
<th>Parasitic</th>
<th>Fungal</th>
<th>Micobact.</th>
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<tbody>
<tr>
<td>T cells</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>B cells</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NK/NKT cells</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMN cells</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MN cells</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Complement</td>
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### Infectious Diseases Susceptibility Primary Immunodeficiency

- **MSMD** *(Mendelian Susceptibility to Mycobacterial Diseases)*
  - IFNGR1
  - IFNGR2
  - IL12B
  - IL12RB1
  - STAT1
  - NEMO
  - TYK2

IFNγ/IL-12/23 pathway
Infectious Diseases Susceptibility
Primary Immunodeficiency

Macrophages

T and NK lymphocytes

IFNγ/IL-12/23 pathway

IFNγ/IL-12/23 pathway
BCG in Primary Immunodeficiencies

IL-12Rβ1 deficiency

Journal of Infectious Diseases 200, 799-812
Biologic era in IBD management: Mucosal Healing


Cellular Pathogenesis of Crohn’s Disease and Approaches to its Treatment

- IL-12/IL-23 Specific Antibodies
- NF-κB inhibitors
- TNF-Specific Inhibitors
- Epithelium
- Commensal bacteria
- Cellular Pathogenesis of Crohn’s Disease and Approaches to its Treatment
- IL-12
- MHC
- TCR
- Retinoic Acid,
- TGF-β
- Treg cell
- Th17 effector T cell
- Th1 effector T cell
- DC
- TGF-β/IL-10
- Macrophage
- Neutrophil
- IL-6
- IL-1β
- TNF
- IFN-γ
- TNF
- IL-17
- Anti-T Cell Antibodies
- Enhancers of Treg Function
- Innate Immune Response Modifiers
- Integrin or Chemokine Receptor Inhibitors
- Mesenteric Lymph node
- Th1 or Th17
- Treg
- Peyer’s patch
- Lamina Propria
- Response Modifiers