New Immunomodulators and Invasive Fungal Infections

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It starts with a case…

- 59 y/o female with AML, s/p matched unrelated donor alloBMT, refractory GvHD, steroids & Infliximab
- Occasional hemoptysis, no fever
- Receiving:
  - Linezolid
  - Moxifloxacin
  - Voriconazole
  - Cefpodoxime
What are we dealing with?

Finger Bx: Mucor
Newer Immunomodulators: an expanding list

- Anti-TNF Ab
- Anti-integrin Ab
- Alemtuzumab (Campath-1H)
- Other anti-lymphocytic agents
- Revlimid
Fungal Infections: Limitation of the Literature

- Isolated cases
- Small series, heterogeneous patient populations
- Potential overreporting or underreporting of events (FDA’s AERS is a passive reporting system)
- Unconfirmed diagnoses
- Absence of a control population
- Imprecise calculations of event rates
- Concomitant immunosuppression
Impairment of Pattern Recognition Molecules

- Complement
- Acute phase reactants
- Immunoregulators

Natural Killer Cells

- Deficiency of circulating NK cells
- Dysfunction of NK cells

Phagocytic Cells

- Deficiency of circulating neutrophils, monocytes
- Defects of phagocytic function

Barriers

- Breakdown of skin/mucosal integrity
- Changes in endogenous flora
- Indwelling vascular catheters

Cell-Mediated Immunity

- Deficiency of circulating lymphocytes
- Imbalance and depletion of lymphocyte subsets
- Aberration of function

Antibodies

- Deficiency of B cells
- Deficiency of Ig production

Cell-Mediated Immunity

- CD4 + Th-cell
- Macrophage
- CD8 + Th-cell (cytotoxic)
- Viral-infected cell

Mycobacterium tuberculosis
Atypical mycobacterium
Legionella spp.
Listeria monocytogenes
Salmonella typhi
Nocardia

Candida spp.
Endemic fungi
Cryptococcus neoformans

P. jiroveci
Toxoplasma gondii
Cryptosporidium
Leishmania

Herpes simplex
Varicella zoster
Cytomegalovirus
HHV-6
Epstein-Barr
Adenovirus
Polyomaviruses
Influenza
Parainfluenzae
RSV

College matrix
Infected macrophage
Granoloma

TNF-α
TNF-α

- Formation and maintenance of granulomas
- Migration and maturation of inflammatory cells to the site of infection
- Production of
  - cytokines such as IL-1, IL-6, IL-8
  - Monocyte chemoattractant protein type-1
  - Adhesion molecules such as intercellular adhesion molecule-1 and E-selectin
TNF-α

Pattern-recognition receptors
- Enhanced TLR-4 expression
- Fungal antigen recognition by neutrophils and antigen-presenting cells
- Activation of endothelial cells

Recruitment of antifungal effector immune cells
- Increased production of inflammatory mediators: INF-γ, IL-1β, IL-1, IL-6, chemokines, EAM, etc.
- Activation of T-cells, monocytes, macrophages, NK cells, neutrophils
- Activation of T-cells, endothelial cells

Infection containment
- Intracellular killing
- Granuloma formation and maintenance

TNF-α blockade
- ↓ Expression of pattern-recognition receptors
- ↓ IFN-γ production, ↑ monocyte apoptosis
- Failure to maintain granuloma

Figure: R Lewis
TNF-α inhibitors: Indications

- Reduce disease severity in
  - Rheumatoid arthritis
  - Crohn’s disease

- Varying efficacy
  - Juvenile rheumatoid arthritis
  - Spondyloarthritis
  - Psoriasis
  - Hidradenitis suppurativa
  - Steroid-refractory graft-versus-host disease reactions in allogeneic hematopoietic cell transplant patients
  - Sarcoidosis
  - Wegener’s granulomatosis
Anti-TNF-\(\alpha\) Ab therapies

- Biologic agents targeting TNF-\(\alpha\)-mediated immunomodulatory effects
  - Infliximab (Remicade): chimeric IgG1\(\kappa\) monoclonal antibody
  - Etanercept (Enbrel):
    - Protein composed of two p75TNF-\(\alpha\) receptors fused to the Fc portion of IgG1
    - Binds both TNF-\(\alpha\) and lymphotoxin-\(\alpha\)
  - Adalimumab (Humira): fully humanized IgG1\(\kappa\) monoclonal antibody
# Pharmacology

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life</th>
<th>Dosing</th>
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<tbody>
<tr>
<td>Infliximab</td>
<td>8-9.5 days</td>
<td>every 15-60 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
</tr>
<tr>
<td>Etanercept</td>
<td>4-5 days</td>
<td>every 3-4 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SQ</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>12-14 days</td>
<td>every 7-14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SQ</td>
</tr>
</tbody>
</table>
Serious side effects

- Lymphoma
- Heart failure
- Granulomatous infections: tuberculosis attack rate was deemed high enough to lead to formal recommendations regarding skin testing in all patients before initiation of infliximab treatment
Immunity against fungi

- Exposure to a fungal antigen
- Naïve T cells differentiate into distinct Th cell subsets
  - Th1 cells: IFN-γ, IL-2, lyphotoxin, and stimulates cell-mediated effector responses and IgG2a production
  - Th2 cells: IL-4, IL-5, IL-9, IL-13, mastocytosis, eosinophilia, IgE, IgG1
- Expression of Toll-like receptor 4 (TLR-4)
  - Important for recognition of fungi including *Candida albicans* and *Aspergillus fumigatus*
Infliximab use in allogeneic BMT patients with severe GvHD

Table 5. Infections after infliximab

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>No. patients (%)</th>
<th>No. positive cultures (%)</th>
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</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive</td>
<td>11 (52)</td>
<td>32 (37)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>5 (24)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (19)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus spp</td>
<td>6 (29)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Candida giabrata</td>
<td>5 (24)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Candida spp</td>
<td>4 (19)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Viral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>11 (52)</td>
<td>16 (18)</td>
</tr>
<tr>
<td>Respiratory viruses</td>
<td>5 (24)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Others</td>
<td>3 (14)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>21 (100)</td>
<td>87 (100)</td>
</tr>
</tbody>
</table>


Literature, 1999 to mid-2006

- 251 reported cases of IFI associated with TNF-α inhibition
  - 215 (86%) associated with infliximab
  - 36 (14%) with etanercept
  - None associated with adalimumab
- Median age 59 years (IQR: 49-70)
- 64% were male

Other Immunosuppression

- Use of at least one other immunosuppressant medication, typically a systemic corticosteroid, was reported during the course of the fungal infection in 86 (99%) of the 87 patients for whom data were available.

Invasive fungal infections

- Aspergillus
- Zygomycetes
- Candida
- Cryptococcus
- Sporothrix
- Histoplasma
- Blastomyces
- Coccidioides

Invasive fungal infections

- Histoplasmosis (n = 78, 31%)
- Candidiasis (n = 62, 25%)
- Aspergillosis (n = 59, 24%)
- Cryptococcosis (n = 25); pneumonias
- Coccidioidomycosis (n = 21)
- Zygomycosis (n = 2)
- Blastomycosis (n = 2)
- Survival 53/80 (66%)

59 cases of aspergillosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>GvHD after HSCT</td>
<td>15</td>
<td>“grave prognosis”</td>
</tr>
<tr>
<td>RA</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>IBD</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

● Is the poor outcome of opportunistic IFIs following TNF inhibition is alloBMT a reflection to profound net state of immunosupression in these patients or it is specifically related to these agents?

● Is the risk outcome of IFIs following TNF blockade dependant on the underlying disease?
Pathophysiology of aGvHD

Acute GvHD

Methylprednisone (MP) 2 mg/kg + tacrolimus

Response 3-7 days into MP?

Yes (50%)

Steroid taper

No

ATG

Pentostatin (adenoside deaminase)
Daclizumab (anti-IL-2 receptor)
Visilizumab (anti-CD3)
Infliximab (anti-TNF-α)
Denileukin diftitox (anti-IL-2, dip toxin)
ECP

# Infliximab and PCP: review of 84 cases

Kaur et al.  
Dig Dis Sci.  
2007;52(6):1481-4

<table>
<thead>
<tr>
<th>Section</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>27</td>
</tr>
<tr>
<td>Women</td>
<td>47</td>
</tr>
<tr>
<td>Mean age = 55 ± 15 years</td>
<td></td>
</tr>
<tr>
<td><strong>II. Indications for infliximab</strong></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>49</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>14</td>
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<tr>
<td>Ulcerative colitis</td>
<td>2</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>2</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>2</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>1</td>
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<tr>
<td>Dermatomyositis</td>
<td>1</td>
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<tr>
<td>Polymyositis</td>
<td>1</td>
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<tr>
<td>Still’s disease</td>
<td>1</td>
</tr>
<tr>
<td><strong>III. Concomitant immunosuppressants</strong></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>38</td>
</tr>
<tr>
<td>Prednisone</td>
<td>37</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>6</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>6</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>5</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>4</td>
</tr>
<tr>
<td><strong>IV. Comorbid diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
</tr>
<tr>
<td>Asthma</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>2</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2</td>
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</tbody>
</table>
PCP Post Infliximab: Temporal Relationship

Mean time between infliximab infusion and onset of symptoms of pneumonia
Number of infusions before onset of symptoms

Mortality: 23/84 pts (27%)

High risk scenarios for IFI following TNF blockade

- GvHD
- History of IFIs
- Colonization with pathogenic fungi
- Environmental exposures
  - High risk travel in endemic areas
  - High risk outdoor activities
  - Construction
Conclusions

- Increased risk of serious IFIs
- Risk, timing for IFIs differs among anti-TNF drugs (infliximab >> etarnacept, adalimumab)
- Could be reactivation of latent infection or progression of newly acquired IFI
- Impossible to calculate specific risk for IFIs or the period at risk for IFIs (no laboratory surrogate marker, no ascertainment of exposure periods)

Bongartz et al. JAMA. 2006 May 17;295(19):2275-85
Recommendations

- High index of suspicion
- No anti-TNF agents in patients with active IFI
- Patients with history of IMIs: Contraindications for anti-TNF agents vs prophylaxis + intense monitoring
- Develop pharmacovigilence database
- Study immunopathogenesis
Other Immunomodulators
Purine Analogue Therapy

- Fludarabine, 2-CdA, Pentostatin, Clofarabine
  - DLT myelosuppression (2-CdA, fludarabine, clofarabine)
    - Advantage: less mucosal, cardiac damage
    - Severe, prolonged CD4+ suppression (<100-200 cells/ml)
      - Less effect seen against CD8+ and NK cells; decreased CD4/CD8 ratio
    - CD4+ improves 1-3 months after therapy, but quantitative abnormalities may persist for up to a year
  - Decrease in B-cell count
  - Transient monocytopenia
Principles of Monoclonal Antibody-Based Therapy

- **ADCC**
  - Antibody dependent cell-mediated cytotoxicity
- **CDC**
  - Complement-dependent cytotoxicity
- **Direct effect on tumor cells**
  - Growth inhibition
  - Cell cycle arrest
  - Induction of apoptosis
- **Synergy with conventional chemotherapies**
Campath-1H (alemtuzumab)

- Lyses lymphocytes via:
  - Antibody dependent cell mediated cytotoxicity
  - Induction of apoptosis

CD52
FC Receptor

Complement

Campath

Effector cell
Median CD4 Cell Counts Over Time (alemtuzumab)
Campath Case 1

- 61 y/o woman with CLL,
- 9/7/04: CMV Ag 205 → 28 → 3
- 10/5/04: GCV level 6.4; 8 → 5 → 1 → 0
- 12/4/04: CXR interstitial opacities
Campath Case 1

- 12/4/04: BAL + PCP
- 1/12/05: GCV level 11.4
- 1/17/05: panc mod aRjxn; CMV HP -
- 1/26/05: Eye fluid + Qual CMV PCR
- 2/05: Ag 2 \(\rightarrow\) 1; bone marrow CMV PCR –
- 5/25/05: Sphenoid sinus Cx + MAI-C
- 6/2/05: BCx + MAI-C
- 6/06: expired from CLL
Infectious complications with alemtuzumab

- Early experience in CLL patients
  - Opportunistic infections in 10/24 pts (42%)
    - 4 episodes of PCP
    - Disseminated VZV
    - Invasive aspergillosis
    - CMV
    - Legionella
    - 2 orbital *Candida* infections

Infectious complications with alemtuzumab

- A small trial (n=24) found that infections were the major toxicity
  - HSV reactivation 38%
  - Oral candidiasis (17%)
  - Pneumonia (21%) - 2 were PCP
  - Bacteremia in 3 pts

**TMP/SMX prophylaxis recommended in all patients receiving alemtuzumab**

Infectious complications with alemtuzumab

* Fludarabine-refractory CLL (n=94) using TMP/SMX prophylaxis
  - CMV reactivation (n=7)
  - PCP in pt. not taking TMP/SMX (n=1)
  - *Aspergillus* (n=2), *Zygomycosis* (n=1)
  - pulmonary cryptococcosis (n=1), invasive candidiasis (n=1)
  - *Listeria meningitis* (n=1)
* Average 4-7 treatments

CMV reactivation at MDACC with alemtuzumab

- Heavily pre-treated CLL patients
- CMV reactivation rate consistently 20-25% across all protocols
- Most common manifestation:
  - Persistent fever on broad spectrum antimicrobials, organ involvement uncommon

? Predisposes for subsequent IFIs
CLL

- 44 year old with CLL
- Refractory to fludarabine
- 6 wks after alemtuzumab
- fever >40°C
- asthenia
- ANC = 80 cells
- Skin biopsy
- Cryptococcus neoformans in blood, urine and stools
- IV lip AmB & 5FC

PCP

- 19 patients with immunodeficiency syndromes (without AIDS)
  - Diagnosed with granulomatous Pneumocystis infection
- Index case: 75-year-old woman with CLL treated with alemtuzumab 3 x weekly for 12 wks.
  - After completion of therapy: dyspnea, hypoxemia, and bilateral infiltrates
  - Responded well to trimethoprim-sulfamethoxazole

Conclusions

- Increased risk of serious IFIs
- Risk, timing for IFIs differs among anti-TNF drugs (infliximab >> etarnacept, adalimumab)
- Also at risk for PCP, CMV, Mycobacteria
- **TMP/SMX prophylaxis, CMV surveillance recommended in all patients receiving alemtuzumab**
- Could be reactivation of latent infection or newly acquired infection
- Cannot calculate specific risk for infections
- High index of suspicion
- No immunomodulatory agents in patients with active infections