New Immunomodulators and Invasive Fungal Infections

Jo-Anne H. (van Burik) Young, MD, FACP, FIDSA
Dimitrios P. Kontoyiannis, MD, ScD, FACP, FIDSA
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
  - Cefpodoxime
  - Posaconazole
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

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

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


Immunosuppression associated with cancer chemotherapy
Cell-Mediated Immunity

CD4 + Th-cell

Macrophage

CD8 + Th-cell (cytotoxic)

Viral-infected cell

College matrix

Infected macrophage

Granuloma

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
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
  - Spondyloarthritides
  - Psoriasis
  - Hidradenitis suppurativa
  - Steroid-refractory graft-versus-host disease reactions in allogeneic hematopoietic cell transplant patients
  - Sarcoidosis
  - Wegener’s granulomatosis
Anti-TNF-α Ab therapies

- Biologic agents targeting TNF-α-mediated immunomodulatory effects
  - Infliximab (Remicade): chimeric IgG1κ monoclonal antibody
  - Etanercept (Enbrel):
    - Protein composed of two p75TNF-α receptors fused to the Fc portion of IgG1
    - Binds both TNF-α and lymphotoxin-α
  - Adalimumab (Humira): fully humanized IgG1κ monoclonal antibody
Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Half-life</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>8-9.5 days</td>
<td>every 15-60 days IV</td>
</tr>
<tr>
<td>Etanercept</td>
<td>4-5 days</td>
<td>every 3-4 days SQ</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>12-14 days</td>
<td>every 7-14 days 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, lymphotoxin, 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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></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><strong>Fungal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Aspergillus</em> spp</td>
<td>6 (29)</td>
<td>7 (8)</td>
</tr>
<tr>
<td><em>Candida glabrata</em></td>
<td>5 (24)</td>
<td>5 (6)</td>
</tr>
<tr>
<td><em>Candida</em> spp</td>
<td>4 (19)</td>
<td>6 (7)</td>
</tr>
<tr>
<td><strong>Viral</strong></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><strong>Total</strong></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

Tsiodras & Kontoyiannis: Fungal Infections Complicating TNF-α Blockade Therapy: A Review of Reported Cases. IDSA 2006
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.

Tsiodras & Kontoyiannis: Fungal Infections Complicating TNF-α Blockade Therapy: A Review of Reported Cases. IDSA 2006
Onset of IFI after TNF blockade

- **Infliximab**
  - Median of 55 days (IQR, 15-140 d)
  - 3 infusions (IQR, 2-5)

- **Etanercept**
  - Median of 144 days (IQR, 46-240 d)

Tsiodras & Kontoyiannis: Fungal Infections Complicating TNF-α Blockade Therapy: A Review of Reported Cases. IDSA 2006
Invasive fungal infections

Tsiodras & Kontoyiannis: Fungal Infections Complicating TNF-α Blockade Therapy: A Review of Reported Cases, IDSA 2006
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%)

Tsiodras & Kontoyiannis: Fungal Infections Complicating TNF-α Blockade Therapy: A Review of Reported Cases, IDSA 2006
Survival

Aspergillus, Candida, Histoplasma, Coccidioides, Sporothrix, Protothecosis

Tsiodras & Kontoyiannis: Fungal Infections Complicating TNF-α Blockade Therapy: A Review of Reported Cases, IDSA 2006
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>

Tsiodras & Kontoyiannis: Fungal Infections Complicating TNF-α Blockade Therapy: A Review of Reported Cases, IDSA 2006
• Is the poor outcome of opportunistic IFIs following TNF inhibition in 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 GvHD

Acute GvHD

Methylprednisolone (MP) 2 mg/kg + tacrolimus

Response 3-7 days into MP?

Yes (50%)
- Steroid taper

No
- ATG
  - Pentostatin (adenosine deaminase)
  - Daclizumab (anti-IL-2 receptor)
  - Visilizumab (anti-CD3)
  - Infliximab (anti-TNF-α)
  - Denileukin diftitox (anti-IL-2, dip toxin)
  - ECPhotophoresis

Rheumatoid arthritis
Meta-analysis

- Randomized, placebo-controlled trials of the 2 licensed anti-TNF antibodies (infliximab and adalimumab) used for 12 weeks or more.

- Nine trials
  - 3493 patients received anti-TNF antibody
  - 1512 patients received placebo

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

- **Malignancy**
  - POR = 3.3 (95% CI, 1.2-9.1)
  - Malignancies were significantly more common in patients treated with higher doses compared with patients who received lower doses
  - Number needed to harm was 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months.

- **Serious infection**
  - OR = 2.0 (95% CI, 1.3-3.1)
  - Number needed to harm was 59 (95% CI, 39-125) for serious infections within a treatment period of 3 to 12 months.

Bongartz et al. JAMA. 2006 May 17;295(19):2275-85
### Infliximab and PCP: review of 84 cases

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

<table>
<thead>
<tr>
<th>I. Demographics</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Indications for infliximab</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>49</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>14</td>
</tr>
<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>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>1</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>1</td>
</tr>
<tr>
<td>Still’s disease</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Concomitant immunosuppressants</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV. Comorbid diseases</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>
PCP Post Infliximab: Temporal Relationship

Mean time between infliximab infusion and onset of symptoms of pneumonia

21 ± 18 days \((n = 40)\)

Number of infusions before onset of symptoms

2.1 ± 1.3 \((n = 76)\)

Mortality: 23/84 pts (27%)

Conclusions RE: TNF blockade

- Increased risk of serious IFIs
- Risk, timing for IFIs differs among anti-TNF drugs (infliximab >> etanercept, 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
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
Recommendations for new courses of TNF blockade

- High index of suspicion
- No anti-TNF agents in patients with active IFI
- Patients with history of mold infections: Contraindications for anti-TNF agents vs prophylaxis & intense monitoring?
- Develop pharmacovigilence database
- Study immunopathogenesis
Other Immunomodulators
Principles of Monoclonal Antibody-Based Therapy

- Cytotoxicity
  - 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
Chimeric murine/human antibody

Binds specifically to CD20 antigen on normal and malignant pre-B and mature B lymphocytes

- CD20 expressed by >90% of B-cell NHL
- No CD20 on human stem cells, progenitor cells, or normal plasma cells

Lyses lymphocytes via:

- Antibody dependent cell mediated cytotoxicity
- Induction of apoptosis

Rituxan (Rituximab)
Rituxan- Immune suppression

- Results in a 90% reduction in peripheral B-lymphocyte counts in 3 days
  - Recovery occurs slowly over 9-12 months

- Despite B-cell depletion, minimal decrease in serum immunoglobulin levels, and no effect on serum complement

- Neutropenia may be seen if used with fludarabine

- Infection incidence and severity is often less than seen with other therapies
Campath-1H (alemtuzumab)

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

- Effector cell
- CD52
- FC Receptor
- Campath
- Complement

Effector cell
Median CD4 Cell Counts Over Time (Campath-1H, alemtuzumab)
**CLL**

- 44 year old with CLL
- Refractory to fludarabine
- 6 wks after alemtuzumab (Campath-1H)
- fever >40°C
- asthenia
- ANC = 80 cells
- Skin biopsy
- *Cryptococcus neoformans* in blood, urine and stools
- IV lip AmB & 5FC

Infectious complications with Campath-1H / alemtuzumab

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

Infectious complications with Campath-1H / alemtuzumab

- This 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 Campath-1H / alemtuzumab

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

PCP

- 19 patients with immunodeficiency syndromes (without AIDS)
  - Diagnosed with granulomatous Pneumocystis infection
- Index case: 75-year-old woman with CLL treated with Campath-1H / alemtuzumab 3 x weekly for 12 wks.
  - After completion of therapy: dyspnea, hypoxemia, and bilateral infiltrates
  - Responded well to trimethoprim-sulfamethoxazole

OIs

- 547 organ transplant recipients
- At least 1 dose of alemtuzumab

Peleg et al. CID 2007;44:204-12.

<table>
<thead>
<tr>
<th>OI</th>
<th>No. (%) of OIs</th>
<th>Time to infection(a)</th>
<th>No. of Ols among transplant recipients receiving alemtuzumab(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>62 (100)</td>
<td>84 (2–328)</td>
<td>16</td>
</tr>
<tr>
<td>Viral</td>
<td></td>
<td></td>
<td>Induction</td>
</tr>
<tr>
<td>CMV disease</td>
<td>16 (26)</td>
<td>85 (7–254)</td>
<td>4</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>GI infection</td>
<td>8</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>3</td>
<td>...</td>
<td>2</td>
</tr>
<tr>
<td>Febrile viral syndrome</td>
<td>1</td>
<td>...</td>
<td>0</td>
</tr>
<tr>
<td>EBV disease</td>
<td>3 (5)</td>
<td>95 (42–288)</td>
<td>2</td>
</tr>
<tr>
<td>PTLD</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Febrile syndrome</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV-negative PTLD</td>
<td>2 (3)</td>
<td>24, 169(c)</td>
<td>0</td>
</tr>
<tr>
<td>HHV-6 infection</td>
<td>1 (2)</td>
<td>222</td>
<td>0</td>
</tr>
<tr>
<td>BK virus infection</td>
<td>12 (19)</td>
<td>134 (18–328)</td>
<td>5</td>
</tr>
<tr>
<td>Parvovirus infection</td>
<td>1 (2)</td>
<td>325</td>
<td>0</td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>12 (19)</td>
<td>51 (2–265)</td>
<td>1</td>
</tr>
<tr>
<td>Cryptococcal infection</td>
<td>2 (3)</td>
<td>54, 200(d)</td>
<td>2</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>1 (2)</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>1 (2)</td>
<td>87</td>
<td>0</td>
</tr>
<tr>
<td>Scedosporium infection</td>
<td>2 (3)</td>
<td>57, 66°</td>
<td>0</td>
</tr>
<tr>
<td>Bacterial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocardia</td>
<td>4 (6)</td>
<td>74 (54–96)</td>
<td>0</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>3 (5)</td>
<td>77 (63–323)</td>
<td>1</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Nontuberculous</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Parasitic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>1 (2)</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>Balanomithia mandrillusani</td>
<td>1 (2)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Recipients with an OI after receiving alemtuzumab (n = 56)</td>
<td>Recipients without an OI after receiving alemtuzumab (n = 491)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>51 (18–77)</td>
<td>51 (16–82)</td>
<td>...</td>
</tr>
<tr>
<td>Sex, female</td>
<td>28 (50)</td>
<td>195 (40)</td>
<td>1.5 (0.9–2.6)</td>
</tr>
<tr>
<td>Transplant received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>16 (29)</td>
<td>235 (48)</td>
<td>0.4 (0.2–0.8)</td>
</tr>
<tr>
<td>Liver</td>
<td>8 (14)</td>
<td>152 (31)</td>
<td>0.4 (0.2–0.8)</td>
</tr>
<tr>
<td>Lung or heart/lung</td>
<td>12 (21)</td>
<td>44 (9)</td>
<td>2.8 (1.4–5.6)</td>
</tr>
<tr>
<td>Pancreas or kidney/pancreas</td>
<td>6 (11)</td>
<td>44 (9)</td>
<td>1.2 (0.5–3.0)</td>
</tr>
<tr>
<td>Intestinal or multivisceral</td>
<td>14 (25)</td>
<td>16 (3)</td>
<td>9.9 (4.5–21.7)</td>
</tr>
<tr>
<td>Previous transplant received</td>
<td>8 (14)</td>
<td>72 (15)</td>
<td>0.9 (0.4–2.1)</td>
</tr>
<tr>
<td>Alemtuzumab received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For induction therapy</td>
<td>16 (29)</td>
<td>338 (69)</td>
<td>0.2 (0.1–0.3)</td>
</tr>
<tr>
<td>For rejection therapy</td>
<td>40 (71)</td>
<td>153 (31)</td>
<td>5.5 (3.0–10.0)</td>
</tr>
<tr>
<td>Doses of alemtuzumab received, no. (range)</td>
<td>2 (1–5)</td>
<td>1 (1–5)</td>
<td>2.3 (1.7–3.1)</td>
</tr>
<tr>
<td>Received pulse methylprednisolone (^a)</td>
<td>15 (27)</td>
<td>152 (31)</td>
<td>0.8 (0.4–1.5)</td>
</tr>
<tr>
<td>Received (&gt;2) pulses of methylprednisolone (^a)</td>
<td>10 (18)</td>
<td>49 (10)</td>
<td>2.0 (0.9–4.1)</td>
</tr>
<tr>
<td>Received another lymphocyte-depleting antibody (^b)</td>
<td>28 (50)</td>
<td>117 (24)</td>
<td>3.2 (1.8–5.6)</td>
</tr>
<tr>
<td>Received both pulse methylprednisolone and another lymphocyte-depleting antibody</td>
<td>7 (13)</td>
<td>55 (11)</td>
<td>1.1 (0.5–2.6)</td>
</tr>
<tr>
<td>Received dacluzimab</td>
<td>2 (4)</td>
<td>7 (1)</td>
<td>2.6 (0.5–12.6)</td>
</tr>
<tr>
<td>CD4 cell count, median cells/mm(^3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>427</td>
<td>589</td>
<td>...</td>
</tr>
<tr>
<td>First month</td>
<td>6</td>
<td>4</td>
<td>...</td>
</tr>
<tr>
<td>First 3 months</td>
<td>11</td>
<td>8</td>
<td>...</td>
</tr>
<tr>
<td>First 6 months</td>
<td>13</td>
<td>21</td>
<td>...</td>
</tr>
<tr>
<td>Second 6 months</td>
<td>139</td>
<td>95</td>
<td>...</td>
</tr>
<tr>
<td>Death (^c)</td>
<td>12 (21)</td>
<td>31 (6)</td>
<td>4.1 (1.9–8.4)</td>
</tr>
<tr>
<td>Allograft failure (^d)</td>
<td>16 (29)</td>
<td>62 (13)</td>
<td>2.8 (1.5–5.2)</td>
</tr>
</tbody>
</table>
Transplant recipients who receive alemtuzumab for rejection
- also exposed to other potent immunosuppressive agents
- more likely to develop allograft failure than were transplant recipients who did not (27% vs. 7%; \( P < .0001 \))
- inherently further out from transplantation & may not have been receiving the same intensive antimicrobial prophylaxis

No association with CMV found

Peleg et al. CID 2007;44:204-12.
Adult renal transplant

- 49 adult renal transplant patients receiving Campath-1H
  - May 1, 2003 and June 7, 2004
  - Mean follow-up = 13.7 months (range, 10-24 months)
- 8 / 49 (16%) patients in the Campath group had an infectious complication, compared to 18 out of 56 (32%) in the historical group
  - 1 case of CMV viremia
  - 2 cases of CMV disease (pneumonitis and enteritis)
  - 4 cases of UTI
  - 1 cellulitis
  - 1 cryptococcal meningitis

Campath Case 1

- 51 y/o woman with diabetes since the age of 10.
  - Gastroparesis.
  - Hypertension. Status post CVA x 2.
  - Chronic kidney disease with a GFR that runs around 40.
  - Coronary artery disease, atrial fibrillation s/p cardioversion.

- History of seizures when she had hypoglycemic unawareness.
  - Suicidal prior to her pancreas transplant.

  - Campath when ALC > 200 for steroid-free IS
Campath Case 1

- 51 y/o woman is CMV IgG +
- 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 → 1; bone marrow CMV PCR –
- 5/25/05: Sphenoid sinus Cx + MAI-C
- 6/2/05: BCx + MAI-C
- 6/06: expired from acute leukemia
CMV Infections

University of Minnesota Pancreas Transplants

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campath CI-</td>
<td>140</td>
<td>8%</td>
</tr>
<tr>
<td>Control</td>
<td>266</td>
<td>5%</td>
</tr>
</tbody>
</table>

P = 0.0001

Figure: R Gruessner
Campath Case 2

- 33 y/o man with diabetes for 21 years.
  - Nonproliferative diabetic retinopathy.
  - Epiretinal membranes in both eyes.
  - Anemia.
- Pancreas transplant in November 2004, from deceased donor.
  - Campath when ALC > 200 for steroid-free IS
- February 2005 *Pseudomonas* peritonitis. Followup CT scan of the abdomen demonstrated peripancreatic fluid and phlegmonous changes in March 2005.
Campath Case 2

- 33 y/o man DM, CMV IgG -, k 5/04
- 11/04 R CMV IgG -, donor panc IgG+
  - Valcyte prophylaxis
- 5/3/05: 426 cells, valcyte to IV GCV
- 5/20/05: 1298 cells
- 5/25/05: Foscarnet initiated
Campath Case 3

- 54 y/o man, diabetes mellitus type 1 since childhood with underlying neuropathy, retinopathy requiring retinal photocoagulation, and previous nephropathy.
  - Hypothyroidism.
  - Hypertension.
  - Focal coronary disease. Angiography done on 11-25-03 showed a focal 50-60% stenosis in the mid LAD, a 30% stenosis of the bifurcation of OM1 and OM2, and there were also two focal 50% lesions in the PDA.
- Simultaneous living related donor kidney with deceased donor pancreas graft, which is enterically drained, in July 2004.
Campath Case 3

- 54 y/o man DM, CMV IgG neg 7/6/04
  - LRD kid & dd panc 7/04
  - Valcyte prophylaxis
- 5/05: BPRPR, Hgb 10, on valcyte
- 5/17/05: random colon bx +HP CMV
- 155 cells; Foscarnet initiated
- 642 – 24 – 6 – 0 – 0 – 0 – 8 – 1
- IgG 444 -> IV IG -> 1090
- Sudden BRBPR at home, xlap
Campath Case 4

- Diabetes mellitus type 1.
  - Proliferative retinopathy.
  - Peripheral neuropathy.
  - Intractable gastroparesis.
  - HTN. CAD, status post PTCA with stenting.
- Seropositive for hepatitis C.
  - BK virus nephropathy.
- Status post pancreas transplant with bladder drainage 7/01, converted to enteric drainage 3/03.
- 11/04-12/04: nodular skin rash
  - *M. simiae/interjectum*
Campath Case 4

- Campath for steroid-free IS July 2001
- CMV duodenitis based on positive biopsies in June 2002.
- 10/30/03: CMV Ag 14 → 3 → 0 → 0 → 0 → 0
- 2/4/05: 4 → 5 → 0 → 0 → 0 → 66 → 24 → 5 → 2
- 5/10/05: liver mass PTLD
- 8 → 0 → 1 → 0; GCV level 5.8; 1 → 1 -> 0 – 0 – 0
- Comfort care
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
Anakinra
Recombinant human IL-1 receptor Ab

Alefacept

- Human lymphocyte function-associated antigen fusion protein
- Psoriasis
- Mycobacterium avium complex olecranon bursitis

Natalizumab

- Humanized monoclonal antibody
- Binds to the α4 chain of the α4β1 and α4β7 integrins
- In multiple sclerosis, the rationale for natalizumab therapy is the reduction of leukocyte extravasation into the CNS by specifically targeting α4β1 or very-late-activation antigen 4.
- PML has developed in several patients with MS
- Role of α4β1-integrin inhibition by natalizumab in the re-expression of JCV from latent sites and in the inhibition of entry into the brain and peripheral sites.

Treatment of PML induced by Natalizumab

Existing interventions
• Antiviral treatment
• Immunomodulatory therapies
• Hematopoietic growth factors
• Plasma exchange
• IV IG
• Leukapheresis and autotransfusion of leukocytes

Experimental therapies
• Small interfering RNA
• In vivo use of antiserum
• Recombinant natalizumab-blocking molecules

Efalizumab

- Anti-CD11a antibody
  - Atopic dermatitis
  - Discoid lupus erythematosus
  - Psoriasis
  - Sjogren's syndrome
- Associated adverse events
  - Lymphoproliferative disease
  - Thrombocytopenia
  - Exacerbation of pityriasis rubra pilaris
Anti–IL-2 receptor antibodies

- Basiliximab, Daclizumab
- *Mycoplasma hominis* septic arthritis in hip 2 months following cadaveric renal transplant
  - Basiliximab
  - Prednisone
  - Tacrolimus
  - Mycophenolate mofetil
  - Thymoglobulin

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 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