**Online A**

**Infectious Complications of Monoclonal Antibody Therapies**

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**DISCLOSURES**

- **Off-Label Usage**
  - None

- **Financial Relationships with Relevant Commercial Interests**
  - None

Resolution: N/A

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**LETTING YOU BOLDLY GO... WHERE YOU WERE NOT SUPPOSED TO GO**

Overall pretty safe

- Injection site reactions (local and angry)
- Infusion reactions (fever, hypotension, often with steroids)
- Almost never given alone (RA, cancer, Crohn’s)
- Lymphoma risk may be increased

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**GENERIC ISSUES**

**HOW TO THINK ABOUT BIOLOGICS?**

- Cytokine blocking
- Lymphocyte depleting
- Adhesion blocking
- Direct anti-cancer

**CYTOKINE BLOCKING**

- TNF alpha
- IL-1
- IL-2
- IL-5
- IL-6
- IL-12p40
- IL-17
- IFNγ
**TNF ALPHA BLOCKADE**

What TNF does: fever, acute phase response  
Uses: RA, Crohn’s, GVH, psoriasis.  
Surface bound TNF issues  
Agents:  
- Etanercept  
- Infliximab  
- Adalimumab  
- Certolizumab  
- Golimumab  
- Enbrel  
- Remicade  
- Humira  
- Cimzia  
- Simponi

**WHAT TNF BLOCKADE SHOULD DO**

**SEVERAL WAYS TO BLOCK TNF**

Soluble Receptor  
Blocking Antibodies  
Soluble Fab fragment

**TNF BLOCKADE INFECTIONS:**

**INTRACELLULAR ORGANISMS (ABOUT 250/10⁵)**

- Mycobacteria  
- Tuberculosis and NTM  
- Histoplasma capsulatum  
- Candida species  
- Listeria monocytogenes  
- Aspergillus species  
- Cryptococcus species  
- Nocardia species  
- Salmonella species  
They break down granulomata.

**IL-1 BLOCKADE**

What IL-1 does: fever, acute phase response  
Uses: RA, autoinflammatory syndromes  
Agents:  
- Anakinra  
- Rilonacept  
- Canakinumab  
- Kineret  
- IL-1 TRAP  
- Ilaris
WHAT IL-1 BLOCKADE SHOULD DO

IL-1: SOMETHING FOR EVERYONE

SEVERAL WAYS TO BLOCK IL-1

IL-1 BLOCKADE INFECTIONS

CYTOKINE BLOCKING

LYMPHOCYTE DEPLETION SHOULD...

IL-2Ra daclizumab, basilizumab
IL-5 mepolizumab
IL-6 tocilizumab
IL-12/23p40 ustekinumab
IL-17 secukinumab

Injection site reactions are common
Upper respiratory infections
Higher doses may be a bigger issue
More infections may appear later?

CD4+ T-cell activation
Th17 differentiation
dendritic cell maturation
NK cell activation
B-cell activation
adaptor activity
<table>
<thead>
<tr>
<th>LYMPHOCYTE DEPLETING: T CELLS</th>
<th>LYMPHOCYTE DEPLETING: B CELLS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alemtuzumab</strong> (CAMPATH, CD52)</td>
<td><strong>Rituximab</strong> (Rituxan, CD20)</td>
</tr>
<tr>
<td>Lymphoma, leukemia, BMT</td>
<td>CLL, lymphoma, SLE, RA, MG</td>
</tr>
<tr>
<td><strong>Antithymocyte globulin</strong> (ATG, T cells)</td>
<td><strong>Ibritumomab</strong> (Zevalin, CD20)</td>
</tr>
<tr>
<td>BMT, aplastic anemia</td>
<td>Rituximab resistant lymphoma</td>
</tr>
<tr>
<td><strong>Alefacept</strong> (Amevive, CD2)</td>
<td>Infections: PML, HBV reactivation</td>
</tr>
<tr>
<td>Psoriasis, CD4 depleting</td>
<td>Occasional hypogammaglobulinemia, but CD20 is not on plasma cells</td>
</tr>
<tr>
<td><strong>Muromonab</strong> (OKT3, CD3)</td>
<td></td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td></td>
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<tr>
<td>Infections: viral (CMV), bacterial, fungal, including PCP; especially CAMPATH</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADHESION BLOCKING</th>
<th>WHY PML?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natalizumab</strong> (Tysabri, $\alpha_4\beta_1$ and $\alpha_4\beta_7$)</td>
<td><img src="image1.png" alt="Diagram" /></td>
</tr>
<tr>
<td>MS, Crohn’s</td>
<td>Prevents entry of T-cell into CNS by blocking integrins</td>
</tr>
<tr>
<td><strong>Efalizumab</strong> (Raptiva, CD11a; pulled from market 2009)</td>
<td>Natalizumab ( $\alpha_4\beta_1$)</td>
</tr>
<tr>
<td>Psoriasis, Crohn’s</td>
<td>Block integrins</td>
</tr>
<tr>
<td>Infections: PML</td>
<td>Inflammmatory bowel and CNS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADHESION BLOCKING: IPILIMUMAB</th>
<th>ADHESION BLOCKING: IPILIMUMAB BLOCKS T CELL INACTIVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ipilimumab</strong> (Yervoy, CTLA4)</td>
<td><img src="image2.png" alt="Diagram" /></td>
</tr>
<tr>
<td>Melanoma, other forms of cancer</td>
<td></td>
</tr>
<tr>
<td>Infections: derepression of tolerance</td>
<td>Inflammmatory bowel and CNS</td>
</tr>
<tr>
<td>Inflammatory bowel and CNS</td>
<td></td>
</tr>
<tr>
<td><strong>Abatacept</strong> (Orencia, CTLA4Ig)</td>
<td></td>
</tr>
<tr>
<td>RA, JRA</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Not much</td>
</tr>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
ADHESION BLOCKING: ABATACEPT BLOCKS T CELL ACTIVATION

ANTICANCER

Gemtuzumab (Myelotarg, CD33)
Uses: AML

Bevacizumab (Avastin, anti-VEGF)
Uses: ocular for retinopathy, solid tumors
Infections: postoperative bowel rupture, wound dehiscence, poor wound healing (~1%)

ANTICANCER: BEVACIZUMAB

Impairs postoperative neovascularization

ANTICANCER

Remember!

Anticytokine autoantibodies happen:
- IFN\(^\gamma\) disseminated OI
- EPO pure red cell aplasia
- IL-6 staphylococcal infections
- G-CSF Felty syndrome
- GM-CSF pulmonary alveolar proteinosis
- IL-17 severe mucocutaneous candidiasis

CONCLUSIONS

These gifts may keep on giving
get a good history.
Not all biologics are the same; know them.

TNF blockers and CAMPATH big players
PML can complicate several modalities

MONOCLONAL ANTIBODIES AND INFECTIONS

- Cytokine Blocking
  - Anti-Tumor necrosis factor (Etanercept, Infliximab, others)
    * Uses: rheumatoid arthritis, Crohn’s, graft-vs-host
  - Anti-Interleukin (interferon-gamma, TNF, IL-1, IL-6, IL-12, GM-CSF)
    * Mycobacteria, Hbs, Crypto, Listeria, Nocardia, Salmonella, Aspergillus

- T Lymphocyte Depleting
  - Alemtuzumab (Campath, others)
    * Infections: Pneumocystis, CMV, EBV, PJP

- B Lymphocyte Depleting
  - Rituximab, others
    * Uses: Rheumatoid arthritis, autoimmune, ITP, Lymphoma, HIV
    * Infections: PML, HBV Reactivation
    * Poor response to immunization

- Adhesion Blocking
  - Natalizumab, others
    * Uses: Multiple sclerosis, Crohn’s
    * Infections: PML

- Anticancer
  - Anti-VEGF (vascular endothelial growth factor,)
  * Complications: Poor Wound healing, wound dehiscence
### MONOCONAL ANTIBODIES AND INFECTION

- **Pre-Therapy Evaluation**
  - Not testable
  - Logical: PPD prior to anti-TNF
  - HBV prior to Rituximab
- **Prophylactic antimicrobials**
  - No clear consensus-not testable
  - Infections and tumors occur but rate uncertain
  - HBV suppression for Rituximab
  - TB chemoprophylaxis (Rx for latent disease) for anti TNF
- **Diagnostic Evaluation for Infection**
  - Depends on specific monoclonal antibody used

### INFECTIONS AND MONOCLONAL ANTIBODIES

#### THREE MOST LIKELY QUESTIONS

- **Anti B Cell**
  - Rituximab
  - PML, HBV Reactivation
- **Anti-TNF Antibody**
  - Etanercept, Infliximab
  - Tuberculosis or Histoplasmosis
- **Anti-Adhesion**
  - Natalizumab (Multiple Sclerosis, Psoriasis, Crohn’s)
  - PML (Progressive Multifocal Leukoencephalopathy)

### REFERENCES


