Infectious Complications of Biologic Therapy

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Generic Issues

• Overall, quite safe
• Injection site reactions (local and angry)
• Infusion reactions (fever, hypotension)
• Almost never given alone (IBD, RA, cancer)
• Certain infections may occur after therapy
• Lymphoma risk *may* be increased
• Keep in mind
  – Mechanism of action to predict risk of adverse events
  – Dose and duration impact vulnerability
How to Think about Biologic Response Modifiers (BRM)?

1. Cytokine blocking agents
   - TNF Alpha: used in autoimmune diseases
     • **Infliximab (Remicade), Adalimumab (Humira), Certolizumab, Etanercept (Enbrel)**
   - Others: IL-1, IL-2, IL-5, IL-6, IL-12p40, IL-17, IFNg
     • IL-1 Anakinra, Rilonacept
     • IL-2 Basiliximab, Daclizumab
     • IL-6 **Tocilizumab (Actemra)** (for RA)
   - They do not destroy leukocytes so more selective than older immune-suppressive agents

Available in Lebanon
How to Think about Biologic Response Modifiers (BRM)?

2. Lymphocyte depleting:
   - Anti CD-52: Alemtuzumab (Campath); lymphopenia
   - Complement inhibition (e.g. Eculizumab, anti C5); disseminated encapsulated organisms

3. Direct anti-cancer
   - Monoclonal antibodies: Rituximab (Rituxan) (anti CD-20), bevacizumab (Avastin), Cetuximab (Erbitux), Trastuzumab (Herceptin)
   - Biologic agents: proteosome inhibitors (Bortezomib, Velcade)
   - Toxin-linked agents: anti CD-20, CD-30

4. Adhesion blocking: Natalizumab (Tysabri), used in MS. Risk of PML

Available in Lebanon
Biologic Response Modifiers (BRM)

• The good... (on target):
  – Treatment of the underlying disease *rather precisely*
    • Autoimmune
    • Oncologic

• The bad ... (off target):
  – Regimen toxicity and infection are limitations

• The *interesting*... our job
Burgeoning of Use for Autoimmune Diseases and Beyond

- GI (IBD mostly Crohn’s Disease)
- Neurology (MS)
- Rheumatology (RA, SLE)
- Pulmonary Medicine (Asthma)
- Endocrinology (DM)
- Psychiatry (Depression)

- RCT of Infliximab for treatment-resistant depression*
  (TNF antagonism does not have generalized efficacy in treatment-resistant depression but may improve depressive symptoms in patients with high baseline inflammatory biomarkers.)

*JAMA Psychiatry 2013:7:31-41
GI Indications of Anti-TNF Therapy

ACG and European Guidelines recommend infliximab in patients with
- Mild-to-moderate disease that is GC-refractory or GC-dependent despite adequate doses of an immunomodulator
- Intolerable adverse events with immunomodulating medications
- Severe disease in whom standard treatment has failed
- Severe UC who require high dose GC or admission

So let’s talk about the more common BRM, those available in this country, and those with well-described and established risks.
# Infliximab (Remicade®) and the Tuberculosis Aftermath

Keane J et al. NEJM 2001;345:1098-1104

<table>
<thead>
<tr>
<th>N</th>
<th>70</th>
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</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>57 (18-83)</td>
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<tr>
<td>Indication (%)</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>47 (67)</td>
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<tr>
<td>Crohn’s Disease</td>
<td>18 (26)</td>
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<tr>
<td>Other</td>
<td>5 (7)</td>
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<tr>
<td>Recent Immunosuppression (%)</td>
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<tr>
<td>Methotrexate + Steroids</td>
<td>28 (40)</td>
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<td>Steroids alone</td>
<td>14 (20)</td>
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<td>Methotrexate alone</td>
<td>6 (9)</td>
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<tr>
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<td>Median weeks to diagnosis (range)</td>
<td>12 (1-52)</td>
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<tr>
<td>Median number of doses (range)</td>
<td>3 (1-9)</td>
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<tr>
<td>Clinical Presentation (%)</td>
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<td>Extrapulmonary, not disseminated</td>
<td>23 (33)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>22 (31)</td>
</tr>
<tr>
<td>Extrapulmonary, disseminated</td>
<td>17 (24)</td>
</tr>
<tr>
<td>Not reported</td>
<td>8 (11)</td>
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</table>
Infliximab and the Tuberculosis Aftermath

- TB is an important complication with BRM
- Note: Extrapulmonary in a significant number of cases, not necessarily ‘typical’
- Often after therapy for a prolonged period of time, not after few doses
- How to gauge the risk?
Invasive Fungal Infection (IFI) associated with GVHD & Infliximab

• IFI also emerged in the context of other immune suppression (HSCT, GVHD)
• Significant attack rate with TNF blockers: 19%
• So abrogation of the immune system by the TNF blockers is after all not as surgical as we’d like it to be

<table>
<thead>
<tr>
<th>Pathogen, type of infection</th>
<th>Infliximab group</th>
<th>Etanercept group</th>
<th>Rate ratio</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>(n = 233,000)</td>
<td>(n = 113,000)</td>
<td></td>
<td></td>
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<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>335 (143.8)</td>
<td>39 (34.5)</td>
<td>4.17</td>
<td>&lt;.001^a</td>
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<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>39 (16.7)</td>
<td>3 (2.7)</td>
<td>6.30</td>
<td>&lt;.001^b</td>
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<tr>
<td><em>Candida</em> species</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>38 (16.3)</td>
<td>8 (7.1)</td>
<td>2.30</td>
<td>.006^b</td>
</tr>
<tr>
<td>NS</td>
<td>26 (11.2)</td>
<td>7 (6.2)</td>
<td>1.80</td>
<td>.065^b</td>
</tr>
<tr>
<td>Systemic</td>
<td>10 (4.3)</td>
<td>1 (0.9)</td>
<td>4.85</td>
<td>.046^b</td>
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<tr>
<td><em>Listeria</em> species</td>
<td>36 (15.5)</td>
<td>2 (1.8)</td>
<td>8.73</td>
<td>&lt;.001^b</td>
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<tr>
<td><em>Mycobacterium</em> species (NS)</td>
<td>30 (12.9)</td>
<td>7 (6.2)</td>
<td>2.08</td>
<td>.023^b</td>
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<tr>
<td><em>Aspergillus</em> species</td>
<td>29 (12.4)</td>
<td>10 (8.8)</td>
<td>1.41</td>
<td>.17^b</td>
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<td><em>Cryptococcus</em> species</td>
<td>11 (4.7)</td>
<td>8 (7.1)</td>
<td>0.67</td>
<td>.91^b</td>
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<tr>
<td><em>Nocardia</em> species</td>
<td>10 (4.3)</td>
<td>1 (0.9)</td>
<td>4.85</td>
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<tr>
<td><em>Salmonella</em> species</td>
<td>7 (3.0)</td>
<td>4 (3.5)</td>
<td>0.85</td>
<td>.75^b</td>
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<tr>
<td><em>Toxoplasma</em> species</td>
<td>5 (2.1)</td>
<td>0 (0)</td>
<td>...</td>
<td>.088^b</td>
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<tr>
<td><em>Brucella</em> species</td>
<td>2 (0.9)</td>
<td>0 (0)</td>
<td>...</td>
<td>.38^b</td>
</tr>
<tr>
<td><em>Bartonella</em> species</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>...</td>
<td>.62^b</td>
</tr>
<tr>
<td><em>Leishmania</em> species</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>...</td>
<td>.62^b</td>
</tr>
<tr>
<td><em>Mycobacterium leprae</em></td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>...</td>
<td>.62^b</td>
</tr>
<tr>
<td>Overall</td>
<td>556 (238.6)</td>
<td>83 (73.5)</td>
<td>3.25</td>
<td>&lt;.001^a</td>
</tr>
</tbody>
</table>
Risk of Infection

- Infliximab used alone has a safety profile comparable to other modes of immune modulation in CD
  - Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study
- Infection risk increases when used with other drugs such as steroids
- Combinations of immune-suppressive therapies in IBD are associated with incremental increase in the relative risk of OI

*Fidler et al. Gut, 2009;58:501-8
More Papers on Infection Risk

- Many studies have been published
- Viral infection may be increased as well
  - Difficult to diagnose and assess
  - Zoster: slight increase in incidence above the background attack rate of 1% in seniors
  - Hep B: associated with viral rebound
  - Hep C: no increase in VL or end-organ disease
  - Use in the setting of chronic viral hepatitis requires caution as they increase LFT’s
- E.g. of case reports: Listeria meningitis cases from Leb
- No increase in hospitalization for Infection after TNFi*

Winthrop KL et al. JAMA 2013: 309;887-95
*Grijalva. JAMA 2011;306:2331
**Rituxan® (Rituximab)**

- Monoclonal antibody directed at CD-20, a B-lymphocyte marker
  - Immunologic effect is depletion of B-lymphocytes
  - Functionally leads to inability to mount Ab response to new antigens and diminished response to recall Ag
  - Impact on humoral immunity:
    - Diminished response to vaccines: proven for influenza vaccine
    - Hypogammaglobulinemia: more common with intensive ritux therapy (esp. with maintenance).
- FDA approved for tx of certain lymphomas and chronic leukemia. Non-FDA approved for GVHD, PTLD, etc...

Rituximab and Infection

- Pre-marketing trials showed no increase in infection in the general NHL population treated with rituximab vs. non-ritux regimens
- Mostly observed in HIV patients with CD4<50 treated with ritux for NHL
- Several case reports linking ritux with specific opportunists: PCP, CMV, VZV reactivation, PML
- Definitively associated with
  - Increased risk of Hepatitis B virus reactivation
  - Increased severity of babesiosis in exposed patients

HBV Reactivation

Epoxure
- Perinatal
- Percutaneous
- Sexual

Acute HBV Infection
- HBsAg+
- HBV DNA+

Resolved HBV Infection
- HBsAg+ → HBsAb+
- HBV DNA neg

Chronic HBV Infection
- HBsAg+ > 6 months
- HBV DNA+

Reactivated HBV Infection
- HBsAg+
- HBeAb+ → HBeAg
- HBV DNA high
- Abnormal LFT’s

Inactive Carrier
- HBsAg+
- HBeAg+ → HBeAb+
- HBV DNA low (or neg)

Chronic Active Infection
- HBsAg+
- HBV DNA+
- Elevated LFT’s

Rituximab
Rituximab & HBV Reactivation in HM

- Risk of HBV reactivation is higher in inactive carriers (HBsAg +) than in patients with resolved HBV
  - In one study, 80% of HBsAg+ NHL patients treated with RCHOP developed reactivation as compared to 55% treated with CHOP (so ritux increases risk further)
  - Timing of reactivation in the absence of antiviral prophylaxis is early— can occur within days

- Risk of reactivation in patients with ‘resolved’ HBV infection can be considerable
  - In one study of HBcAb+ NHL patients, 24% treated with RCHOP developed reactivation vs. NONE treated with CHOP
  - Timing of reactivation in HBcAb+ patients is later than with inactive carrier (majority developed HBV reactivation by 2-5 months after ritux containing chemo finished)

Rituximab and HBV Reactivation

• Clinical outcomes
  – Fulminant hepatic failure and death (reported in inactive carriers and HBcAb+ patients)

• Prevention:
  – All patients in whom rituximab therapy is planned should be screened for HBV (using Core Ab and possibly DNA)
  – Antiviral prophylaxis is typically given to inactive carriers (most data with lamivudine)
  – Management of HBcAb+ patients varies
    • At least one recent study has advocated for prophylaxis
    • Guidelines advocate for close monitoring for reactivation

Meta-analyses of RCTs to Quantify Infectious Risk of BRM

- Reviewed many studies, and pooled 9 (n=3493)
  - Infliximab 3-10 mg/Kg q4-8 ≥ weeks
  - Adalimumab 20-40 mg/wk q1-2 weeks ≥ wks
  - Challenges: different studies (design, risks, definitions)

- Infection: OR 2 for serious infection

- Malignancy (e.g. lymphoma, SCC)
  - OR 3.3 (1.2-9.1)

Bonartz T, JAMA 2006; 295:2275-85
• Another meta-analysis 2012 showed the risk of increased malignancy does not hold
• 63 RCTs with 29,423 patients, followed for at least 24 weeks and analyzed.
  – No statistically significant increased risk of developing malignancy was observed.
  – Of the 29,423 patients, 211 developed a malignancy during the trial. No statistically significant risk was observed for specific cancer sites
• CONCLUSION: The use of BRMs among patients with RA included in RCTs of at least 6 months' duration was not significantly associated with an increased risk of malignancy compared with other disease-modifying antirheumatic drugs or with placebo.

* Lopez-Olivio, JAMA 2012;308:898-908
What to do if they do develop an infection e.g. TB?

• Case reports
• Treat both, done safely and concomitantly
• When the immune modulator is stopped, IRIS may occur which may complicate the picture

Matsumoto T et al. NEJM 2006;355:740-741
BRM in Hematologic Malignancy (HM)

- Patients with HM are vulnerable to infectious complications (underlying disease, chemotherapy)
- Many of the reports linking specific opportunists to a specific agent are in case series and case reports (so interpret association carefully)
- Recently approved BRM (belatacept): increased risk of PTLD (1.4%), poor outcome
  - Role of EBV monitoring: not established, no prophylaxis
  - Reduction of immune suppression can be done, but definite management is unclear

Durrbach A et al. Am J Transplant 2010;10:547
So How to Mitigate the Risk?

- **Risk stratification** (e.g. duration of therapy, other immune compromising conditions and drugs, co-morbid diseases)
- Evaluate for **tuberculosis** exposure (CXR, IGRA if the patient is already immunosuppressed because a TST may be inconclusive)
- **Screen for viral infections:**
  - **Hepatitis B:** HBsAb, HBsAg, HBcAb
  - Screen for other viral infections: Serology for CMV, HSV, EBV, VZV, HIV
  - No evidence that hepatitis C is reactivated by these drugs
- **Viral monitoring** based on risk: EVB, CMV, BK, PCR.
  - No established guidelines for this

So How to Mitigate the Risk?

• Vaccination: non-live vaccination only
  – Pneumococcus, influenza, HPV
  – Consider meningococcal vaccination if anti C5 (eculizumab, rituximab)
  – Evaluate household contacts for vaccination
  – Live vaccines: Contraindicated during BRM therapy and for at least the first 3 months after discontinuation of treatment

• Consider antimicrobial prophylaxis: Case by case (high risk)
  – PCP if other risk factors exist*
  – Amoxicillin with rituximab and if IgG is low
  – Acyclovir
  – Antifungal

• Be aware, be suspicious when you see patients who received these drugs

*Harigai M et al. NEJM 2007;257:1874-76
So in Conclusion...

- BRM therapy has given us an improved ability to treat certain diseases, but at the risk of increased infection.
- The UPSIDE: improved control of IBD, RA, decreased rates of rejection and better graft function over time.
- The DOWNSIDE: A slight increase in complications from therapy, hence the need for screening and prevention prior to initiation of those agents, and vigilance once the patient has received them.
Thank You all for your attention