Disclosures:
Advisory boards, speaker, clinical trials.....

- Amgen
- Merck
- Pfizer
- Novartis
- BMS
- UCB
- Roche
- Abbvie
- Celgene
- Janssen
Objectives

1. To review indications and rationale for using biological agents in Rheumatic inflammatory disorders.
2. To be aware of potential complications of Biologic drugs.
3. To improve comfort and skill level in recognizing special situations that may arise when using these agents.
4. To apply this knowledge to patients that are seen in daily practice who are using these medications.
RA joint deformities: various stages

Early RA

Intermediate RA

Severe RA

How did we get here?
Could it have been avoided?

Prevention of Early Damage
Preserves Function
RA Pathophysiology: Role of T-Cells, B-Cells, & Cytokines
Biologics have revolutionized the treatment of inflammatory arthritis:

Compared to traditional DMARDs →

- Reduced pain, joint swelling, and stiffness
- Improved function, work productivity
- Reduced radiographic destruction
- Reduced cardiovascular events
- Reduced mortality
- Higher remission rates

**All Biologics appear to be more effective when used in combination with Methotrexate**
Biologics in Inflammatory Rheumatic Disease: Indications in Canada

Rheumatoid Arthritis (RA):

Psoriatic Arthritis (PsA) & Psoriasis (PsO)

Ankylosing Spondylitis (AS):

Inflammatory Bowel disease: IBD
# Anti-TNF Biologic Agents

<table>
<thead>
<tr>
<th></th>
<th>Enbrel (Etanercept)</th>
<th>Humira (Adalimumab)</th>
<th>Remicade (Infliximab)</th>
<th>Simponi (Golimumab)</th>
<th>Cimzia (Certolizumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>TNF receptor antagonist</td>
<td>mAb (human)</td>
<td>mAb (chimeric)</td>
<td>mAb</td>
<td>mAb (pegylated)</td>
</tr>
<tr>
<td>T 1/2</td>
<td>4-5 days</td>
<td>12-14 days</td>
<td>8-9.5 days</td>
<td>14 days</td>
<td>14 days</td>
</tr>
<tr>
<td>Route of Admin.</td>
<td>SC</td>
<td>SC</td>
<td>IV</td>
<td>SC/IV</td>
<td>SC</td>
</tr>
<tr>
<td>Dose/ Frequency</td>
<td>50 mg qw 25 mg biw</td>
<td>40 mg q2wks</td>
<td>3-5 mg/kg q8wks</td>
<td>50 mg q4wks</td>
<td>200 mg q2w 400 mg q4w</td>
</tr>
<tr>
<td>RAMQ (med d’exception)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Indications</td>
<td>RA, PsA, AS</td>
<td>RA, PsA, AS, Crohns</td>
<td>RA, PsA, AS, Crohns</td>
<td>RA, PsA, AS</td>
<td>RA, PsA, AS</td>
</tr>
</tbody>
</table>

## Table Notes:
- **MOA**: Mode of Action
- **T 1/2**: Time to half-life
- **Route of Admin.**: SC = Subcutaneous, IV = Intravenous
- **Dose/ Frequency**: qw = Once a week, biw = Every other week, q2wks = Every 2 weeks, q8wks = Every 8 weeks, q4wks = Every 4 weeks
- **RAMQ**: RAMQ (med d’exception) indicates whether the medication is covered by RAMQ for medical exception.
Anti-TNFα Biologics for RA

## Non Anti-TNF Biologic Agents

<table>
<thead>
<tr>
<th></th>
<th>Orencia (Abatacept)</th>
<th>Rituxan (Rituximab)</th>
<th>Actemra (Tocilizumab)</th>
<th>Kineret (Anakinra)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOA</strong></td>
<td>Co-Stimulation T cell</td>
<td>Anti-CD20 B cell</td>
<td>Anti-IL6</td>
<td>IL-1 Ra</td>
</tr>
<tr>
<td><strong>T 1/2</strong></td>
<td>16.5 days</td>
<td>22 days</td>
<td>6 days</td>
<td>4-6 hrs</td>
</tr>
<tr>
<td><strong>Route of Admin.</strong></td>
<td>IV</td>
<td>IV</td>
<td>IV SC</td>
<td>SC</td>
</tr>
<tr>
<td><strong>Dose/ Frequency</strong></td>
<td>500-1000 mg q4w</td>
<td>1000mg q6m</td>
<td>8 mg/kg q4w</td>
<td>100 mg daily</td>
</tr>
<tr>
<td><strong>RAMQ (medi d’exception)</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (for IV)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>RA</td>
<td>RA, Lymphoma</td>
<td>RA, GCA</td>
<td>RA</td>
</tr>
</tbody>
</table>

**Additional Notes:**
- Ustekinimab- for PsA (anti IL-12/23), Secukinimab- for PsA, AS (anti-- IL-17), New oral non- biologic JAK Inhibitor: Tofacitinib for RA
Other Non Anti-TNF “Advanced” Therapies:

**Kevzara (Sarilumab):** IL-6 inhibitor (RA)

**Stelara (Ustekinimab):** IL-12/23 inhibitor (PsA)

**Cosentyx (Secukinimab):** IL-17 inhibitor (PsA, AS)

**Taltz (Ixekizumab):** IL-17 inhibitor - (PsA, AS)

**JAK inhibitors:** Xeljanz (Tofacitinib) - RA, PsA
  Olumiant (Baricitinib) - RA

**Otezla (Apremilast):** PDE4 inhibitor - (PsA)
RA Case:

• 37 yo female, RA for 4 years
• On MTX 25 mg/wk, Plaquinil 400mg/d, prednisone 7.5 mg/d, Ibuprofen 600 mg tid
• 12 swollen joints, CRP 22, HAQ score 1.8
• Erosions on xray, and even more detected on MRI

**This patient is an excellent candidate for addition of Biological agents**
RAMQ Criteria Biologics: RA

• Active disease:
  – >8 swollen joints
  – HAQ >1
  – ↑ CRP
  – Erosions on x-ray

• Despite: >3 months of 2 DMARDs (1 of which being MTX >20mg)
I SHALL DO NO HARM....
Practical Safety Considerations with Biologics

- Infections (serious, opportunistic, TB)
- Malignancies
- Vaccinations
- Pregnancy
- Pre and Peri-op management
- CHF
- Demyelination
- Autoantibodies
- Injection/infusion reactions
Mini Case 1

- 61 year old male with RA, Tx with Adalimumab, MTX, Diclofenac. Presents to ER with cellulitis left leg, WBC 12.2, Temp 38. He is due for Adalimumab SC injection in 2 days.

What should you do?

1. Start Ab’s and tell him to take his Adalimumab as usual.
2. Don’t give Ab’s – they interact adversely with Adalimumab.
3. Start Ab’s and tell him to hold Adalimumab until infection is clear.
4. Advise to stop Adalimumab permanently since it has increased his infection risk.
Serious Infections
Predictors and Risk of Infection in RA

- Relative Risk to general population: 1.9 [1.7 – 2.1]
- Best predictors:
  - RA severity / disease activity
  - Age
  - Corticosteroid therapy
  - Comorbid diseases: CVD, CHF, CRF, DM, lung disease
  - Skin infection
  - Joint surgery
- Contributory role of DMARDs not clearly defined

Serious Infections Rates by Anti-TNF-α Drug vs DMARD in RA Patients: BSR Biologics Registry

<table>
<thead>
<tr>
<th></th>
<th>DMARD n = 1354</th>
<th>ETN n = 3596</th>
<th>IFX n = 2878</th>
<th>ADA n = 1190</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure (PYs)</td>
<td>1352</td>
<td>4075</td>
<td>4618</td>
<td>1175</td>
</tr>
<tr>
<td>No. of infections</td>
<td>56</td>
<td>209</td>
<td>255</td>
<td>61</td>
</tr>
<tr>
<td>Rate of infections per 100 PYs (95% CI)</td>
<td>4.14 (3.14–5.35)</td>
<td>5.13 (4.47–5.85)</td>
<td>5.52 (4.88–6.22)</td>
<td>5.19 (3.99–6.62)</td>
</tr>
<tr>
<td>Adjusted IRR* (95% CI)</td>
<td>Referent</td>
<td>0.97 (0.63–1.50)</td>
<td>1.04 (0.68–1.61)</td>
<td>1.07 (0.67–1.72)</td>
</tr>
</tbody>
</table>

BSR = British Society of Rheumatology, IRR = incidence rate ratio; PY, person-years.
*Adjusted for age, sex, disease severity, comorbidity, extra-articular manifestations, steroid use, and smoking.

- **Crude rates of serious infections were similar for different anti-TNF-α drugs irrespective of drug half-life**
- **Compared with the DMARD-treated cohort, there was no increased risk of all-site serious infection for any of the 3 drugs (except maybe for skin and soft tissue)**

Infections: Anti-TNF Agents

- All TNF antagonists have warnings about serious infections in package insert
- Administration of any of the anti-TNF therapies should be discontinued if the patient develops serious infection or sepsis and should not be initiated in patients with active infection
- Education of Pts. and MD’s is key
Recommended management of anti-TNF biologics in infection

• Simple upper respiratory tract viral infections:
  – No modification of treatment

• More severe viral infection (influenza, herpes zoster…) or severe bacterial infection (fever, bacteremia, systemic infection, recurrent infection…):
  – Anti-TNF therapy should be temporarily discontinued
  – Appropriate antibiotic or antiviral therapy
  – Resumption of anti-TNF after resolution of the infection
Mini Case 2

- 43 year old Asian male with PsA. On MTX, NPXN, HC cream, about to start Etanercept.
  Pre-TNF: CXR n, PPD pos. 7 mm, never received BCG.
  What would you do?

1. Go ahead with Tx – Etan not associated with TB compared to other anti-TNF agents (MAB’s)
2. Tell patient he is too high risk for TB and so should never receive an anti-TNF.
3. Go ahead with Tx- PPD was <10 mm, and so considered negative.
4. Hold Tx temporarily, and give patient INH for 9 months.
Tuberculosis
Tuberculosis in RA

• 4 fold increase of TB incidence in RA
  - varies with geographic area

• General TB risk factors:
  - immunosuppression from medication
  - debilitation
  - aging population
  - migratory movements
  - immunocompromised states
Tuberculosis (TB): Background

- **Animal models**
  - TNF necessary for granuloma homeostasis
  - Inhibition of TNF associated with granuloma disruption

- **In humans**
  - Cases of TB have been seen in patients treated with all the TNF antagonists
  - Commonly extra-pulmonary
  - Great majority of cases felt to represent reactivation
  - Risk factors include concomitant corticosteroids and diabetes
  - Patients should be screened for TB prior to beginning TNF antagonist therapy

### Numbers and rates of incidents tuberculosis, limited to first anti-TNF drug (F/U censored at date of starting second anti-TNF drug)

<table>
<thead>
<tr>
<th>Number of patients ever received drug</th>
<th>DMARD (n=3232)</th>
<th>All anti-TNF (n=10,712)</th>
<th>ETN (n=3913)</th>
<th>IFX (n=3295)</th>
<th>ADA (n=3504)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actively receiving drug, person years (p-yrs)</td>
<td>7,345</td>
<td>23,286</td>
<td>10,111</td>
<td>7,459</td>
<td>5,716</td>
</tr>
<tr>
<td>Cases of TB</td>
<td>-</td>
<td>24</td>
<td>4</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Rate/100,000 p-yrs (95% CI)</td>
<td>-</td>
<td>103 (66,153)</td>
<td>40 (11, 101)</td>
<td>147 (74, 264)</td>
<td>157 (72, 299)</td>
</tr>
<tr>
<td>IRR, adjusted for age, sex and entry year (95% CI)</td>
<td>-</td>
<td>-</td>
<td>Referent</td>
<td>3.7 (1.1, 12.7))</td>
<td>4.4 (1.3, 15.2)</td>
</tr>
<tr>
<td>Most recent drug exposure, person years (p-yrs)</td>
<td>7,345</td>
<td>27,624</td>
<td>11,926</td>
<td>8,963</td>
<td>6,735</td>
</tr>
<tr>
<td>Cases of TB</td>
<td>-</td>
<td>33</td>
<td>6</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Rate /100,000 p-yrs (95% CI)</td>
<td>-</td>
<td>119 (82, 168)</td>
<td>50 (18, 110)</td>
<td>134 (69, 234)</td>
<td>223 (125, 367)</td>
</tr>
<tr>
<td>IRR, adjusted for age, sex and entry year (95% CI)</td>
<td>-</td>
<td>-</td>
<td>Referent</td>
<td>2.7 (0.9, 7.8)</td>
<td>4.4 (1.6, 12.1)</td>
</tr>
</tbody>
</table>

Anti-TNF Agents and Opportunistic Infections

- Opportunistic infections are rare but have been observed in patients on biologic therapies
  - Bacterial, viral, and fungal infections, including histoplasmosis, listeriosis, *Pneumocystis carinii*, cytomegalovirus and herpes zoster\(^1\)-\(^3\)

- Risk may be reduced for etanercept vs anti-TNF monoclonal antibodies\(^1,3\)

\(^2\)www.fda.gov/cder/drug/InfoSheets/HCP/TNF_blockersHCP.htm
\(^3\)Strangfeld A et al. *JAMA* 2009;301:737-44
\(^3\)Maury et al. *Arthritis Rheum* 2005: 52: S347
TB - the bottom line

- Exacerbation of latent TB more common with monoclonal TNF inhibitors (TNFi’s) than fusion proteins
- ~50% have disseminated or atypical presentations
- FDA Black box warning for all TNFi’s
- TB screening and prophylaxis recommended for all patients on TNFi’s
- If latent infection is diagnosed, appropriate prophylaxis guidelines should be instituted, usually INH for 9 months.
- Note that a PPD of >5mm is considered positive for screening rather than the traditional 10 mm.
Issues with TB screening and Latent TB Prophylaxis in RA

• Active RA patients anergic (up to 30%)
  – Negative TB skin test may not exclude latent TB infection
  – Ethnic diversity, frequent BCG vaccination history
  – two step TB skin test if suspicion high
• Fear of combining INH with MTX
• When to add anti-TNF Tx to MTX + INH

INH isoniazid
MTX methotrexate
Review

Guidance for the management of patients with latent tuberculosis infection requiring biologic therapy in rheumatology and dermatology clinical practice

Fabrizio Cantini\textsuperscript{a,*}, Carlotta Nannini\textsuperscript{a}, Laura Niccoli\textsuperscript{a}, Florenzo Iannone\textsuperscript{b}, Giovanni Delogu\textsuperscript{c}, Giacomo Garlaschi\textsuperscript{d}, Alessandro Sanduzzi\textsuperscript{e}, Andrea Matucci\textsuperscript{f}, Francesca Prignano\textsuperscript{g}, Michele Conversano\textsuperscript{h}, Delia Goletti\textsuperscript{i}, on behalf of SAFEBIO (Italian multidisciplinary task force for screening of tuberculosis before and during biologic therapy)
TB Screening Algorithm

**BCG-unvaccinated**
- TST and IGRA
  - TST-negative
    - IGRA-negative
      - Annual SCREENING with TST and/or IGRA in those considered at high risk of TB exposure*
  - TST and/or IGRA-positive

**BCG-vaccinated**
- IGRA
  - IGRA-positive
  - IGRA-negative
    - Chest X-rays
      - Active TB excluded. Education on TB. Preventive therapy for LTBI
        - INH 5mg/Kg/day/6mo. or INH 5mg/Kg/day/3mo AND Rif 10 mg/Kg/day/4mo or Rif 10 mg/Kg/day/4mo.
        - Biologic starting after 1 month
      - IF INH Vit. B6 1 tab/eod
        - Active TB diagnosis. Active TB management.
    - Annual SCREENING with IGRA in those considered at high risk of TB exposure*

---

*Fig. 1. SAFEBio recommendations for LTBI detection and active TB prevention in RA patients before biologic therapy starting.
Mini Case 3

- 62 yo male, just started Golimumab 10 weeks ago for his RA. He heard about the Zoster vaccine and asks if he should get it.

What do you advise?

1. Wait till he is on a stable dose of Gol for at least 3 months and then can receive the vaccine
2. No point to give now since the biologic drug will suppress his ability to respond to the vaccine
3. Do not give- it is a live vaccine and so is contraindicated
## Vaccinations of RA patients

When possible, vaccination should be done prior to Tx

<table>
<thead>
<tr>
<th>Medications</th>
<th>Pneumovax (anti-pneumococcus)</th>
<th>Fluviral (anti-influenza)</th>
<th>Twinrix Engerix Havrix (anti-hepatitis)</th>
<th>Avoid live vaccinations (zoster, rabies, oral polio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCQ (Hydroxychloroquine)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LEF (Leflunomide)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MTX (Methotrexate)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SSZ (Sulfasalazine)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>All Biologic Response Modifiers Agents</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

X: Recommendations

SAAG K. G., American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis Arthritis & Rheumatism Vol. 59 (6), June08, pp 762–784
Live Vaccines

- BCG
- Polio
- Measles
- Mumps
- Rubella
- MMR

- Varivax (varicella)
- Yellow Fever
- Zostavax (zoster)
- Flumist (inhaled influenza vaccine)
Box 1 Recommendations for vaccination in adult patients with AIRD treated with biologics

1. Thorough assessment of vaccination status before beginning treatment with a biologic agent;
2. Vaccination can be administered during therapy with anti-TNF agents, TCZ and ABA but ideally should be given before B cell depleting biologicals are prescribed; and in both cases with the disease stabilised.
3. Live attenuated vaccines should be avoided.
4. The influenza and pneumococcal vaccines are strongly recommended.
5. Tetanus toxoid vaccination should be administered as in the general population, except if the patient has been treated with RTX within the last 24 weeks and is at high risk of developing tetanus, in which case passive immunisation with tetanus immunoglobulin is strongly advised.
6. There are no data to help advice about the use of HZV, HPV, hepatitis A and/or B, Haemophilus influenzae b, meningococcal vaccines and BCG.

ABA, abatacept; AIRD, autoimmune rheumatic diseases; HPV, human papillomavirus; RTX, rituximab; TNF, tumour necrosis factor.

Vaccines and biologics
Isabel Ferreira,¹ David Isenberg²

Ann Rheum Dis, May, 2014
Other Vaccination Considerations

- Shingrix?
- Vaccinate even with live vaccines at time of scheduled biologic injection?
- “High dose” Flu vaccine vs. regular Fluvax for RA patients? (recent McGill study)
Mini Case 4

• 54 yo female with severe RA. Breast cancer diagnosed after 10 months on Etanercept (anti-TNF). Will need Radiotherapy and Chemotherapy. The biologic has “changed her life” w.r.t. pain and function and QOL.

What will you recommend?

1. Never give a biologic to this patient again - too high risk
2. No clear evidence of biologic association with solid tumours, so can continue Tx without worry
3. Hold biologic while patient treated for cancer and plan to restart if patient in remission
4. Switch to a non anti-TNF Biologic agent and continue treating her
Malignancy
**Risk of Malignancies in RA Patients compared to general population: A Systematic Lit. Review**

<table>
<thead>
<tr>
<th></th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total malignancy</td>
<td>1.05</td>
<td>1.01 to 1.09</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2.08</td>
<td>1.80 to 2.39</td>
</tr>
<tr>
<td>Lung</td>
<td>1.63</td>
<td>1.43 to 1.87</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0.77</td>
<td>0.65 to 0.90</td>
</tr>
<tr>
<td>Breast</td>
<td>0.84</td>
<td>0.79 to 0.90</td>
</tr>
</tbody>
</table>

TNF Inhibitors and Risk of Malignancy

US National Data Bank for Rheumatic Diseases¹

- Biologic-treated patients (n = 13,001)
- Overall cancer risk was similar to general population (SIR = 1.0), but biologics were associated with increased skin cancer risk (melanoma and non-melanoma)

SEER, Surveillance, Epidemiology, and End-Results: SIR, standardised incidence ratio; IRR, incidence risk ratio

¹Wolfe F, Michaud K. Arthritis Rheum 2007;56(9):2886-95
²Greenberg J et al. ACR 2007, Abstract 282
## Lymphoma Incidence in RA

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th># RA Patients</th>
<th>Years of follow-up</th>
<th>SIR for Cancer</th>
<th>SIR for Lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gridley (1993)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Sweden</td>
<td>11,683</td>
<td>20</td>
<td>1.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Mellenkjaer (1996)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Denmark</td>
<td>20,699</td>
<td>14</td>
<td>1.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Isomaki (1978)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Finland</td>
<td>46,101</td>
<td>7</td>
<td>1.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Baecklund (1998)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Sweden</td>
<td>11,683</td>
<td>18</td>
<td>–</td>
<td>1.0 (Low act.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.4 (Med act.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25.8 (High act.)</td>
</tr>
</tbody>
</table>

## Anti-TNFα Agents and Lymphoma Risk – National Data Base: USA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Observed Cases</th>
<th>Expected Cases</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treatments</td>
<td>79</td>
<td>45.0</td>
<td>1.8 (1.4–2.2)</td>
</tr>
<tr>
<td>ETN</td>
<td>10</td>
<td>4.0</td>
<td>2.5 (1.4–4.7)</td>
</tr>
<tr>
<td>IFX</td>
<td>27</td>
<td>13.1</td>
<td>2.1 (1.4–3.0)</td>
</tr>
<tr>
<td>ADA</td>
<td>2</td>
<td>0.8</td>
<td>2.4 (0.6–9.6)</td>
</tr>
<tr>
<td>All biologics</td>
<td>35</td>
<td>17.7</td>
<td>2.0 (1.4–2.8)</td>
</tr>
<tr>
<td>DMARDs (no biologics)</td>
<td>36</td>
<td>14.5</td>
<td>2.5 (1.8–3.5)</td>
</tr>
</tbody>
</table>

No increase in risk of lymphoma with anti-TNFα therapy, MTX or combination of both when controlling for disease activity (entry HAQ, number of prior DMARDs and use of prednisone).

Malignancies and Biologics: summary statements

- Risk of solid tumours does not appear to be increased by Biologic meds
- Lymphoma increased, but registry data suggest that it is the disease itself and not the treatment that confers the increased risk
- Skin cancer (Melanoma and NMSC) increased with Biologics
- No clear consensus, but in the context of cancer, need to have a risk/benefit discussion on a case by case basis to decide on Tx
- RTX may be best choice for biologic Tx if previous cancer
Mini Case 5

- 28 yo woman with AS, on adalimumab (anti-TNF). AS much better and now feels well enough to consider family planning.

How should you counsel her?

1. Too risky for an AS flare during pregnancy, so pregnancy not advisable
2. Hold adalimumab for 3 months, then proceed with family planning
3. Continue adalimumab until she confirms she is pregnant and then stop
4. Continue adalimumab throughout pregnancy - no known pregnancy risk
Pregnancy Considerations- A Risk/Benefit Dilemma

• Effect of disease on pregnancy
  – Evidence of poorer outcomes and increased complications (low birth weight, HTN, miscarriage) in IBD, PsO, RA if disease active in pregnancy
  – AGA recommends disease should be in remission prior to conception and to maintain remission throughout

• Effect of drugs on the pregnancy
Safety issues of biologics in pregnant patients with rheumatic diseases

Monika Østensen
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<table>
<thead>
<tr>
<th>TNF-α inhibitor type</th>
<th>Type of studies</th>
<th>Number of human pregnancies exposed</th>
<th>Median percentage of maternal to cord serum level</th>
<th>Effect on pregnancy/child</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab: complete IgG1 antibody</strong></td>
<td>Case reports, cohort studies, case-control, registry data</td>
<td>&gt;1000</td>
<td>160</td>
<td>No increase in miscarriage or malformations; no malformation pattern detected</td>
</tr>
<tr>
<td><strong>Etanercept: fusion protein with Fc part</strong></td>
<td>Case reports, cohort studies, case-control, registry data</td>
<td>&gt;500</td>
<td>6</td>
<td>No increase in miscarriage or malformations; no malformation pattern detected</td>
</tr>
<tr>
<td><strong>Adalimumab: complete IgG1 antibody</strong></td>
<td>Case reports, cohort studies, case-control</td>
<td>&gt;300</td>
<td>179</td>
<td>No increase in miscarriage or malformations; no malformation pattern detected</td>
</tr>
<tr>
<td><strong>Golimumab: complete IgG1 antibody</strong></td>
<td>Registry data</td>
<td>40</td>
<td>not done</td>
<td>Data not conclusive</td>
</tr>
<tr>
<td><strong>Certolizumab: pegylated Fab fragment</strong></td>
<td>Registry data and case reports</td>
<td>139</td>
<td>3.9</td>
<td>No increase in miscarriage or malformations; no malformation pattern detected</td>
</tr>
<tr>
<td>Biologic type</td>
<td>Type of studies</td>
<td>Number of human pregnancies exposed</td>
<td>Effect on pregnancy/child</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------------------</td>
<td>-------------------------------------</td>
<td>----------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Rituximab: complete IgG1 antibody</td>
<td>Case reports, registry data</td>
<td>~200</td>
<td>Preconception and early first-trimester exposure: in a few studies, no harm to child detected; second- and third-trimester exposure: B cell depletion in child</td>
<td></td>
</tr>
<tr>
<td>Abatacept: fusion protein with Fc part</td>
<td>One case report</td>
<td>1</td>
<td>No conclusive human data</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab: complete IgG1 antibody</td>
<td>Case reports (abstracts)</td>
<td>39</td>
<td>No conclusive human data</td>
<td></td>
</tr>
<tr>
<td>Anakinra: IL-1 receptor antagonist</td>
<td>Case reports</td>
<td>3</td>
<td>Animal data: no harm in offspring. No conclusive human data</td>
<td></td>
</tr>
<tr>
<td>Belimumab: complete IgG1 antibody</td>
<td>No published data</td>
<td>83 unpublished</td>
<td>Animal data: no harm in offspring. No conclusive human data</td>
<td></td>
</tr>
</tbody>
</table>
Motherisk Recommendations

• Limited, adequately powered, well-designed studies on safety of medications used in RA
• Balance potential benefits/risk with potential risk associated with untreated moderate-severe RA
• Risk/benefit ratio will vary from case to case

<table>
<thead>
<tr>
<th>Medications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>sulfasalazine, azathioprine,</td>
<td>cumulative data reassuring</td>
</tr>
<tr>
<td>antimalarials</td>
<td></td>
</tr>
<tr>
<td>biologics (adalimumab,</td>
<td>do not appear likely to pose a major</td>
</tr>
<tr>
<td>anakinra, etanercept,</td>
<td>teratogenic risk</td>
</tr>
<tr>
<td>infliximab, certolizumab)</td>
<td></td>
</tr>
<tr>
<td>anti TNF Class B</td>
<td></td>
</tr>
</tbody>
</table>

www.motherisk.org Accessed April 3, 2010
Conclusions: Pregnancy

• More data accumulated over time are required to fully evaluate the safety of anti-TNF agents during pregnancy. Increased placental transport of IgG in 3rd trimester (not for CZP)

Current data suggest that if there is a signal of teratogenicity with anti-TNF agents, it appears small

• Reasonable consensus is to stop biologics once pregnant. Continue during pregnancy only if benefits for a particular case outweigh the risks.
Mini Case 6

67 yo man on adalimumab (anti-TNF) for RA. Booked for a hip replacement (THR).

How do you advise him to deal with the biologic drug?

1. Stop the drug at least 1-2 weeks prior to Sx (depending on T 1/2)
2. No need to stop – no evidence of increased infection risk for elective surgery
3. Time the biologic injection as close to the Sx as possible, since increased disease activity prior to Sx may actually increase the infection risk
4. Stop anti-TNF agent 3 months prior to elective surgery
Biologics in the peri-operative period in RA – theoretical considerations:

• TNF blockade may increase the risk of post-operative infection (by decreasing leucocyte trafficking and neutrophil recruitment)

• May also impair wound healing (by decreasing angiogenesis)
Anti-TNF treatment and risk of surgical site infections after elective orthopedic surgery in RA

768 RA patients: 1,219 elective orthopedic procedures:

<table>
<thead>
<tr>
<th>Procedures, n</th>
<th>anti-TNF naïve patients</th>
<th>anti-TNF treatment interrupted, n</th>
<th>anti-TNF treatment continued, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures, n</td>
<td>1023</td>
<td>104</td>
<td>92</td>
</tr>
<tr>
<td>SSI rates</td>
<td>4.0%</td>
<td>5.8%</td>
<td>8.7%*</td>
</tr>
</tbody>
</table>

- Continuing anti-TNF > interrupted anti-TNF before surgery but not statistically different
- Variables significantly associated with increased risk of SSI in all patients:
  - History of SSI or skin infection
  - Elbow, foot or ankle surgery
  - Steroid Use
  - Diabetes
- Continued perioperative use of anti-TNF was not a strong risk factor for SSI

SSI = serious surgical infection

* p<NS for difference between anti-TNF interrupted and anti-TNF continued
Infection Risk After Orthopedic Surgery in Patients With Inflammatory Rheumatic Diseases Treated With Immunosuppressive Drugs

CATRINA B. SCHERRER,1 ANNE F. MANNION,1 DIEGO KYBURZ,2 MARKUS VOGT,3 AND INÈS A. KRAMERS-DE QUERVAIN1
Table 4. Descriptive statistics and ORs from the multiple logistic regression with the degenerative/posttraumatic group as the reference, adjusted for the propensity score*

<table>
<thead>
<tr>
<th></th>
<th>Degenerative/posttraumatic group</th>
<th>IRD without DMARDs†</th>
<th>IRD + conventional DMARD(s)‡</th>
<th>IRD + TNFα inhibitor‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgeries, no.</td>
<td>47,887</td>
<td>451</td>
<td>756</td>
<td>122</td>
</tr>
<tr>
<td>Infections, no. (%)</td>
<td>373 (0.8)</td>
<td>7 (1.6)</td>
<td>21 (2.8)</td>
<td>7 (5.7)</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)</td>
<td>1.0 (reference)</td>
<td>1.60 (0.75–3.43)</td>
<td>3.41 (2.18–5.34)</td>
<td>6.90 (3.16–15.07)</td>
</tr>
<tr>
<td>*P</td>
<td>0.222</td>
<td>&lt; 0.001</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* OR = odds ratio; IRD = inflammatory rheumatic disease; DMARDs = disease-modifying antirheumatic drugs; TNFα = tumor necrosis factor α; 95% CI = 95% confidence interval.
† Plus or minus corticosteroids.
‡ Plus or minus corticosteroids and/or conventional DMARD(s). For TNFα inhibitor therapy, only if the last dose was taken ≤3 administration intervals prior to surgery.

Highest risk if hold TNF drug less than 1 cycle of usual dosing
TNF Antagonists: Relative Contraindications

- Current active serious infections
- Chronic/recurrent infections
- History of untreated TB and/or positive PPD test
- Systemic lupus erythematosus?
- Multiple sclerosis, optic neuritis
- Congestive heart failure, ?ILD
Conclusions: Safety

- Treatment of Inflammatory disease patients with Biologic therapy is generally safe and well tolerated
- Rare, important events have been seen with all TNF antagonists
  - Serious infections
  - TB and other opportunistic infections (more common with mAb’s)
  - Lymphomas
  - Demyelinating events, CHF, Lupus-like reactions, Hepatic and Hematologic abnormalities
- Screening for TB recommended in all patients
- Updated vaccinations recommended
- Vigilance required re: infectious and malignant complications
- Patient education key
Thank You!