Rheumatology Therapeutics: Perioperative DMARD Management, Infection and Malignancy Risks, Vaccination Considerations

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Objectives

• Know Broad Categories of Rheumatoid Arthritis Medications
• Know when to start and stop DMARDS in the Perioperative Period
• Recognize drugs that may increase risk for infection
• Understand malignancy risks associated with DMARD's
• Know vaccination recommendations for Rheumatic Disease

Perioperative Considerations in Patients with Rheumatic Disease

• When to stop therapy in relation to timing of surgery?
• Do all anti-rheumatic therapies need to be stopped?
• If drug is stopped, will flare impair post-op recovery (ie need for steroids, inability to participate in therapy, etc)
• Are risks of infection and healing increased on DMARDS?
Perioperative Rheumatic Drug Management

- HCQ
- Glucocorticoids
- Methotrexate
- Leflunomide
- SSZ
- Azathioprine
- Biologic DMARDS (Enbrel, Humira, Rituxan, Remicade, etc)
- NSAID’s

Perioperative DMARD Management

- Hydroxychloroquine
  - Antimalarial
  - Works by impairing neutrophil chemotaxis, impairs complement-dependent antigen-antibody reactions

Recommendation: No Need to Stop
Periop DMARD Management

• Corticosteroids:
  – Usually unnecessary to stress dose unless pt on > 5mg/day prednisone or equivalent steroid

  Stress dose according to magnitude of stress:
  Depending on procedure:
  – 50 mg IV hydrocortisone at time of anesthesia induction then 25mg q 8 hours
  – 100 mg of hydrocortisone IV q 8 hours until pt can be switched to regular po dose.

Corticosteroid coverage for surgery in patients taking exogenous corticosteroids

<table>
<thead>
<tr>
<th>Type of Stress</th>
<th>Dosage and Duration</th>
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<tbody>
<tr>
<td>Minor procedures</td>
<td>Take usual morning steroid dose. No extra supplementation is necessary.</td>
</tr>
<tr>
<td>Moderate surgical</td>
<td>- Take usual morning steroid dose. Give 50 mg hydrocortisone intravenously just before the procedure and 25 mg of hydrocortisone every 8 hours for 24 hours. Resume usual dose thereafter.</td>
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<tr>
<td>Major surgical stress</td>
<td>- Take 100 mg of intravenous hydrocortisone before induction of anesthesia, and 50 mg every 6 hours for 24 hours. Taper dose by half per day to maintenance level.</td>
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Periop DMARD Management

• Methotrexate:
  • DHFR inhibitor, inhibits lymphocyte proliferation (folate antagonist), increases adenosine release, modulates cytokine profile
    — Uses: RA, PsA, MCTD

Methotrexate, continued

• Reasons to stop: May impair post-op wound healing?
• Reason to continue without stoppage in peri-op period: sufficient control of the disease is necessary to avoid flares, which may limit postoperative rehabilitation and which would increase the need of other drugs (e.g., corticosteroids)
The place of methotrexate perioperatively in elective orthopedic surgeries in patients with rheumatoid arthritis

Harwig Pieringer, Ulrike Sheib, Georg Bisenbach

Review Article, Clinical Rheumatology, 2008

- Eight papers
- These studies compare continued vs. discontinued MTX therapy or MTX therapy vs. therapies other than MTX.
- Data showed that MTX therapy appears to be safe perioperatively and seems also to be associated with a reduced risk of flares.
Leflunomide

- **Leflunomide:**
  - Use: RA, Psoriasis, other
  - Mechanism: immunodulatory, inhibits pyrimidine synthesis, antiproliferative and anti-inflammatory effects
  - Adverse Reactions: Myelosupression, Hepatotoxicity
  - Long Half-Life: 14-15 days

- **Recommendation:** Hold 2 weeks prior to surgery and resume 3 days postop
Periop DMARD Management

• Sulfasalazine:
  – Use: RA, AS, PsA, IBD-arthropathy
  – 5-Aminosalicylic Acid- modulates inflammatory response, especially leukotrienes, poss free radical scavenger or TNF-inhibitor
  – Can be associated with leukopenia or other cytopenia
• Recommendation:
  – Discontinue 5-7 days preoperatively, resume postop

Periop DMARD Management

• Azathioprine:
  – Use: RA, MCTD, SLE, Myositis
  – Mechanism of Action: Imidazolyl derivative of mercaptopurine; antagonizes purine metabolism and may inhibit synthesis of DNA, RNA, and proteins; interferes with cellular metabolism and inhibit mitosis.
    – Toxicities: Myelosuppression
• Recommendation:
  – Discontinue 5-7 days before surgery, resume post-op
Periop DMARD Management

• NSAID’s:
  – Antiplatelet effect: stop at least three half-lives prior to surgery
    • Ibuprofen: half-life of about 2.5 hours, 1 day prior to surgery,
    • Naproxen, half-life of 15 hours, stop 4 days before
    • Aspirin one week prior to surgery to allow production of new platelets.

Biologic DMARDS

• TNF: Enbrel, Humira, Cimzia, Infliximab
• IL-6: Actemra
• IL-1: Anakinra
• Costimulatory Blockade: Ocrenica
• B lymphocyte: Rituxan
Biologic DMARDS

- Little evidence on what to do
- Review article: Am J Therapeutics
- Data primarily gathered from general surgical patients who have had non-elective surgery and were recently exposed to Biologic
- Increased Skin and Soft tissue infections
Biologic DMARDs

- Recommendation: Wait at least one or two treatment cycles without drug administration prior to elective surgery.
- Enbrel: 1-2 weeks after last treatment
- Humira: 2-4 weeks after treatment
- Simponi/Orencia: Wait 4-8 weeks
- Do not restart any above until wound healing is complete.

Biologic DMARDs

- Important to Remember with respect to surgery:
  - The baseline infection risk is increased 13-fold in individuals with RA when compared with the general population.
Rituximab

- Selectively depletes B cells that bear the CD20 surface marker

Rituxan

- Elective procedures should probably not be scheduled until the B-cell counts have returned to normal.
- Emergent surgery: Prev Rx with Rituxan not absolute C/I but extra vigilance suggested
Safety Considerations of Biologic DMARDs

- Serious Infection and TB
- Lymphoma
- Demyelination
- Hematological abnormalities
- Administration reactions
- Congestive heart failure
- Autoantibodies and Lupus

Targets for RA Therapy

- T-cell activation: (antigen presentation, co-stimulation)
- Inhibition of second signal (CTLA-4-Ig)
- IL-6 and C5 blockade
- Cytokine inhibitors
- Kinases, nitric oxide, matrix metalloproteinases
- Angiogenesis blockade
- Osteoclast disruption
Black Boxes

• “Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Enbrel, Remicade, Humira.”

Challenges

• Underlying disease increases risk
• Other medications may increase risk
• Patients with cancer are excluded from clinical trials
• Long term risk cannot be detected with short term trials
Wolfe 2007
• National Data Bank for Rheumatic Diseases
• 19,591 participants, 89,710 person years
• 55.3% got biologics
• 68.3% got MTX
• Diagnoses of RA were made by rheumatologists.
• Patients diagnosed with lymphoma prior to the beginning of the study were excluded.

The Patients

Table 2. Demographic and clinical characteristics of the 19,591 participants*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age at baseline, mean ± SD years</td>
<td>59.0 ± 13.2</td>
</tr>
<tr>
<td>Male sex</td>
<td>22.8</td>
</tr>
<tr>
<td>Education, mean ± SD years</td>
<td>13.2 ± 2.2</td>
</tr>
<tr>
<td>Disease duration at study start, mean ± SD years</td>
<td>14.1 ± 12.1</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>55.4</td>
</tr>
<tr>
<td>Biologic agent use ever in NDB</td>
<td>55.3</td>
</tr>
<tr>
<td>Infliximab use ever in NDB</td>
<td>40.3</td>
</tr>
<tr>
<td>Etanercept use ever in NDB</td>
<td>19.2</td>
</tr>
<tr>
<td>Adalimumab use ever in NDB</td>
<td>7.6</td>
</tr>
<tr>
<td>Methotrexate use ever in NDB</td>
<td>68.0</td>
</tr>
<tr>
<td>Baseline lifetime DMARD count (0–11 scale)</td>
<td>2.3 ± 1.6</td>
</tr>
<tr>
<td>Prednisone therapy at baseline</td>
<td>45.7</td>
</tr>
<tr>
<td>Methotrexate therapy at baseline</td>
<td>57.7</td>
</tr>
<tr>
<td>Baseline HAQ score, mean ± SD (0–3 scale)</td>
<td>1.1 ± 0.7</td>
</tr>
</tbody>
</table>

* Except where indicated otherwise, values are the percentage. NDB = National Data Base; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire.
Bottom Line

- The study found no association between anti-TNF drugs and lymphoma.
- Also found no association between the concomitant use of anti-TNF with MTX and lymphoma.
- Potential problems exist.

Askling 2009

- Linked Data from multiple Swedish Registries
- 6,366 patient with RA who started TNF inhibitor between 1998 and 2006.
- Drugs: Etanercept, Adalimumab, Infliximab
- Controls:
  - Biologic naïve RA cohort (61,160)
  - RA pts. starting MTX same period (5,989)
  - RA pts. starting combination DMARD therapy (1,838)
  - General Population of Sweden
Bottom Line

- Patients treated with anti-TNF had a cancer risk that was similar to:
  - Anti-TNF–naive RA patients
  - Patients starting MTX therapy
  - Patients starting DMARD combination therapy

- Neither the incidence nor the relative risk of cancer increased with time since first starting anti-TNF therapy nor did they increase with the cumulative duration of active anti-TNF therapy

- None of the 3 anti-TNF agents was itself associated with an increased overall risk of cancer, but each of them displayed different cancer risks during the first year of followup. These differences disappeared.

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Bottom Line

- No evidence of increased risk of most cancers conferred by treatment with anti-TNF agents in RA population.
- Some increase in risk of melanoma.
Discussion: Malignancy Risks

- Rheumatoid arthritis increases risk of cancer, probably due to inflammation over time.
- More severe RA is more likely to get anti-TNF treatment, but is also more likely to lead to cancer development. This makes the studies hard to perform.
- Some think that overall, the anti-TNF drugs may decrease cancers in the long term by decreasing the inflammation.
- One of the difficulties with meta analysis is the heterogeneous nature of the groups in the studies. It can be more difficult to tell with your individual patient.

Jakinibs block multiple aspects of cytokine signaling
Major Toxicities

- Anemia
- Neutropenia
- Infections, especially viral
- Liver function abnormalities
- Lipid abnormalities

Surgery Recommendations:
- No data but half life only 3 hours (bid dosing) so could stop just a few days before and resume once wound closed

Vaccinations in Rheumatic Disease

- Increased risk of infection in all patients, regardless of DMARD status in RA
- Few reports (anecdotal and case reports only) have shown evidence of flare of autoimmune disease after vaccination
CDC recommendations

• When feasible, clinicians should administer all indicated vaccines to all persons before initiation of chemotherapy, before treatment with other immunosuppressive drugs, and before radiation or splenectomy.
• No live, attenuated vaccines*
• Evidence that use of therapeutic monoclonal antibody preparations, especially the Anti-TNF agents adalimumab, infliximab, and etanercept, predisposes persons to other opportunistic infections suggests caution in the use of live vaccines in patients receiving these drugs.

*Recent study suggests that zoster may be safe while on TNF-I therapy

ACIP: advisory committee on immunization practice

ACR & EULAR Recommendations

• All patients: Influenza, Pneumovax
• Tetanus toxoid vaccination: in accordance with recommendations for the general population.
• Vaccines should be administered during a stable period of Rheumatic Disease
• Select Patients with Risk: Hep B, HPV*
• All patients >60 Zoster
• Vaccines can be administered while on nonbiologic and biologic DMARDS but should be administered before initiating B-cell depleting therapy
• *HPV: should probably be given to all young SLE patients <26 yo, higher risk than normal population for invasive cervical cancer
Vaccinations: Special Circumstances

• In case of major and/or contaminated wounds in patients who received Rituximab within the last 24 weeks, passive immunization with tetanus immunoglobulins should be administered.
• If on high dose corticosteroids, wait on live-virus vaccination for at least 1 month
• Patients receiving >20mg/day prednisone should not be given live vaccines

Zoster

• ACR Recommendations:
• Risk in RA elevated: 3 to 14 cases per 1,000 person-years compared with 1.5 to 4 cases per 1,000 in the normal population
  ✓ RA and its therapies may put older patients at risk for shingles; because of their immunosuppressed status, these patients are at greater risk of developing H. zoster and having more severe outcomes.
  ✓ Zoster vaccine should be offered to all RA patients 60 years of age and older, even if they are on MTX and low-dose prednisone
  ✓ Still advisable to avoid the zoster vaccine in patients actively receiving TNF inhibitors, as well as abatacept, rituximab and anakinra.
  ✓ In some, it may be advisable to delay the initiation of biologic therapy until at least two weeks after the zoster vaccine is given.
Zoster

- Defer the zoster vaccine for at least one month after discontinuation of immunosuppressant therapy (high-dose corticosteroids, >20 mg/day of prednisone or the equivalent for two or more weeks)
- For those receiving TNF, defer the vaccine for at least a month after discontinuation of such therapy
- Consider the zoster vaccine for those on short-term corticosteroids (fewer than 20 mg/day of prednisone or equivalent for less than 14 days), those given topical steroids, or those on long-term, alternate-day, low-dose treatment;

Zoster

- ACR Hotline 08/01/2008:
  - RA and its therapies may put older patients at risk for shingles; because of their immunosuppressed status, these patients are at greater risk of developing H. zoster and having more severe outcomes.
  - Rheumatologists should consider giving zoster vaccine to all RA patients 60 years of age and older, even if they are on MTX and low-dose prednisone (especially since many RA patients may ultimately receive biologic agents).
  - Until more research becomes available it is still advisable to avoid the zoster vaccine in patients actively receiving TNF inhibitors, as well as abatacept, rituximab and anakinra.
  - In some, it may be advisable to delay the initiation of biologic therapy until at least two weeks after the zoster vaccine is given.
Zoster Vaccine and Biologic DMARD update, 2012


- Observational study of 463,541 Medicare enrollees ≥ age 60 with autoimmune diseases, including RA (~60%), spondyloarthropathies, psoriasis and inflammatory bowel disease. 633 people were exposed to biologic therapies around the time they received the vaccine, most of who (n=551) were users of anti-TNF biologics. The vast majority of these patients were given the vaccine by non-rheumatologists (e.g. primary care physicians). During the next 6 weeks, the time frame in which any safety concerns would have been expected, there was no increased risk found for zoster or primary varicella infection. This preliminary evidence suggests the possibility that the vaccine might be safe to give to patients receiving treatment with biologics.

Zoster Vaccine and Biologic DMARD update, 2012

- Recent observational data suggests that the effectiveness of the zoster vaccine in a large group of patients with autoimmune diseases, including RA and spondyloarthropathies, is comparable to that in healthy, older patients. In the same study, the vaccine was not associated with short term risks for zoster or varicella, even in patients exposed to biologics around the time they were vaccinated. However, in the absence of a prospective trial, this evidence should not be presumed to supersede the cautions above regarding live virus vaccines in biologic users.
SLE - HPV

- Patients with SLE are at risk of persistent HPV infection.
- The prevalence of abnormal Pap smears and cervical intraepithelial neoplasia (CIN) in SLE patients is higher than that in age-matched healthy women.

Vaccine Response in Rheumatic Diseases

- RA and SLE patients may have a lower immune response to vaccination.
- Pneumococcal and influenza vaccines are considered safe in both SLE and RA patients.
Response to Vaccination on Anti-TNF

- The results overall are mixed:
- Several studies reported responses to influenza and pneumococcal vaccination that were decreased as compared with Controls.
- Greater number of studies reported responses that were comparable to controls.


Medications

- Methotrexate:
  Variable response.
- Hydroxychloroquine:
  No effect on Influzena vaccine in RA and SLE.
- Leflunomide
  No Data
- Azathioprine:
  Variable results.
Rituximab

- 2 main studies:

  - Results:
    - Rituximab reduces humoral responses following influenza vaccination in RA patients, with a modestly restored response 6–10 months after rituximab administration.
    - Previous influenza vaccination in rituximab-treated patients increases pre- and postvaccination titers.
    - RA activity was not influenced.


  - Results:
    - Recall responses to the T cell–dependent protein antigen tetanus toxoid as well as DTH responses were preserved in rituximab-treated RA patients 24 weeks after treatment.
    - Responses to neoantigen (KLH) and T cell–independent responses to pneumococcal vaccine were decreased, but many patients were able to mount responses.
    - **Conclusion:** polysaccharide and primary immunizations should be administered prior to rituximab infusions to maximize responses.
Questions

• Not sure?
  – Call Deschutes Rheumatology