PERIOPERATIVE MANAGEMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS
CANADIAN SOCIETY OF INTERNAL MEDICINE, ANNUAL MEETING 2016

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Professeure agrégée, médecine interne
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Chantal Vallée, October 26\textsuperscript{th} 2016
CONFLICT DISCLOSURE

➤ Definition: A conflict of interest may occur in situations when personal or professional interests of individuals may have actual, potential or apparent influence over their judgement and actions.

➤ No relevant conflict of interest or financial disclosure in regard with this presentation

➤ Speaker fees received in the past three years from Sanofi, Novo Nordisk, Bayer, Merck, AstraZeneca and Boehringer Ingelheim

➤ Dre Chantal Vallée, October 26th 2016
OBJECTIVES

➤ Perform a preoperative assessment of patients with rheumatoid arthritis (RA) and obtain appropriate preoperative tests in this population

➤ Manage immunosuppressive therapy in patients with RA and who are undergoing surgery (e.g. anti-TNF, methotrexate)

➤ Discuss the role of preoperative steroid stress dose in chronic steroid users
TO BEGIN WITH...

➤ 2-3 millions of surgery/year in Canada
➤ Increased complexity of patients
➤ Latest knowledge of and recommendations regarding treatment of specific disease states
➤ Preparing and optimizing patients
➤ Communication between clinicians
OBJECTIVES FOR THE PREOPERATIVE ASSESSMENT

➤ Identify which patients could be at increased risk for surgery
➤ Implement strategies to reduce the risk of surgery
➤ Review (optimize) general state of health
PREOPERATIVE ASSESSMENT

➤ History
➤ Physical examination
➤ Work-out according to risk
  ➤ patient risk
  ➤ surgery risk
WHAT TO ASSESS

➤ Cardiac conditions and risk factors
➤ Pulmonary diseases and risk factors
➤ Endocrine conditions
➤ Hematologic conditions
  ➤ bleeding problems
  ➤ thrombosis conditions and risk factors
➤ Medications
➤ Others
QUESTION #1

➤ Which of the following represent the major risk for surgery in rheumatoid patients?

➤ 1. Infection
➤ 2. Cardiovascular complications
➤ 3. Rheumatoid flare
➤ 4. Pain
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PATIENTS WITH RHEUMATOID DISEASES

➤ 60% of rheumatoid patients will need surgery
➤ Increased cardiovascular risk
➤ Immunosuppression and surgical site infections
➤ Steroid coverage
➤ States of altered coagulation
➤ Prediction of poor pain and function outcomes
  ➤ Disease flare
    ➤ pain and swelling
    ➤ fatigue and inability to participate in activities
CLINICAL SCENARIO

➤ Mrs L.P., 72 years old to be evaluated for an elective hemicolecctomy for diverticular bleeding

➤ Rheumatoid arthritis since age 54
  ➤ leflunomide 200 mg every other day
  ➤ prednisone 10 mg every day
  ➤ infliximab 200 mg every 5 weeks
  ➤ calcium, vitamin D, omeprazole and alendronate

➤ Type 2 diabetes on metformin, 500 mg twice a day, sitagliptine 100 mg every day, NPH 12 units at bedtime
CLINICAL SCENARIO

➤ No chest pain, no shortness of breath

➤ Can climb slowly one flight of 10 stairs

➤ Limited mostly by pain in her knees, but doesn’t feel she would be able to do more without being short of breath

➤ BP 137-85, Pulse 92, weight 62 kg, exam otherwise normal

➤ EKG is normal, A1c 7.5%, creatinine 110
QUESTION #2

➤ What would be your next step?

➤ 1. Order a treadmill test
➤ 2. Order a nuclear stress test
➤ 3. Start bisoprolol at low dose before surgery
➤ 4. Send her for surgery without no more intervention
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PREOPERATIVE CARDIAC ASSESSMENT

➤ Higher risk of cardiovascular disease

➤ RA - SLE

➤ 60% increase in CV death

➤ mortality ratio 1.61 (95% CI 1.48 -1.75, P < 0.0001)

➤ more atypical symptoms of angina
PREOPERATIVE CARDIAC ASSESSMENT

➤ Principles

➤ Intervention is rarely necessary to simply lower the risk of surgery

➤ No test such be performed unless likely to influence management
J Am Coll Cardiol. 2014;64(22):e77-e137. doi:10.1016/j.jacc.2014.07.944
CV RISK ASSESSMENT

1. Is the surgery an emergency?
   - Yes?
     - Proceed

2. Is there active cardiac condition?
   - Yes?
     - Treat and stabilize

3. What is the risk of the surgery?
   - Low risk?
     - Proceed
CV RISK ASSESSMENT

➤ Does the patient have a good functional capacity?
  ➤ Yes?
    ➤ Proceed
  ➤ Challenging here with rheumatoid conditions…
    ➤ Limited activity - marker for increased CV risk
      ➤ Gerson, et al, Annals of Internal Medicine, 1985;103:832-837
CV RISK ASSESSMENT

➤ Presence of CV risk factors?
  ➤ ischemic heart disease
  ➤ heart failure
  ➤ cerebrovascular disease
  ➤ diabetes treated with insulin
  ➤ renal insufficiency

➤ diagnosis of RA, psoriatic arthritis, ankylosing spondylitis or SLE???
J Am Coll Cardiol. 2014;64(22):e77-e137. doi:10.1016/j.jacc.2014.07.944
CLINICAL SCENARIO, PART II

➤ Nuclear stress test shows lateral ischemia, low intensity
➤ Bisoprolol 2.5 mg prescribed

➤ Patient heard about infectious risk
➤ Worried ++
QUESTION #3

➤ Which of the following is responsible for the worst surgical site infection risk?

➤ 1. Infliximab
➤ 2. Leflunomide
➤ 3. Prednisone
➤ 4. Rheumatoid arthritis
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IMMUNOSUPRESSION AND INFECTIOUS RISK

➤ Controversy
➤ Sparse data
➤ Careful risk:benefit analysis
  ➤ type and site of surgery
  ➤ comorbidities
  ➤ previous infections
  ➤ type and dose of immunsuppression
  ➤ risk of disease flare
IN BETWEEN TWO RISKS

- risk of infection
- risk of flare-up
METHOTREXATE

➤ One of the most commonly used
➤ More than 10 studies
  ➤ largest presented by Grennan et al, 2001
  ➤ no increase risk of infection or wound healing
  ➤ more flare-ups in those who stopped 2 weeks before surgery
# Methotrexate

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients (on MTX)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murata et al (2006)</td>
<td>retrospective</td>
<td>124 (80)</td>
<td>continue</td>
</tr>
<tr>
<td>Bibbo et al (2003)</td>
<td>retrospective</td>
<td>104(104)</td>
<td>continue</td>
</tr>
<tr>
<td>Jain et al (2002)</td>
<td>retrospective</td>
<td>80(46)</td>
<td>continue</td>
</tr>
<tr>
<td>Grennan et al (2001)</td>
<td>prospective</td>
<td>388(88)</td>
<td>continue</td>
</tr>
<tr>
<td>Carpenter et al (1996)</td>
<td>prospective</td>
<td>32(13)</td>
<td>withhold</td>
</tr>
<tr>
<td>Escalante et al (1995)</td>
<td>retro/prospective</td>
<td>204(?)</td>
<td>continue</td>
</tr>
<tr>
<td>Kasdan et al (1993)</td>
<td>retrospective</td>
<td>42(15)</td>
<td>continue</td>
</tr>
<tr>
<td>Sany et al (1993)</td>
<td>prospective</td>
<td>64(32)</td>
<td>continue</td>
</tr>
<tr>
<td>Perhala et al (1991)</td>
<td>retrospective</td>
<td>121(80)</td>
<td>continue</td>
</tr>
<tr>
<td>Bridges et al (1991)</td>
<td>retrospective</td>
<td>38(19)</td>
<td>withhold</td>
</tr>
</tbody>
</table>

Adapted from Akkara Veetil and Bongartz, Nature Rheumatology 2012;8:32-41
METHOTREXATE

Recommendation:

SAFE to continue

Canadian Rheumatology Association, 2012 (Level I, Strength A)

Caution if comorbidities (renal, respiratory or hepatic)

could be withheld the week of and the week after the surgery
LEFLUNOMIDE

- Limited data
- Higher rate of postoperative wound-healing
- 1 prospective trial, 82 patients
  - same rate of infection in both group (1 continue, 1 stopped 2 weeks before up to 2 weeks after)
- Long half-life (14 days)

 Recommendation
- NOT to stop
SULFASALAZINE

- Limited data
- Half-life 6-10 hours
- Renal elimination

Recommendation
- To be withheld the day of the surgery if risk of AKI
AZATHIOPRINE

➤ Data in RA and in Crohn’s disease
➤ Not associated with postoperative complication
➤ Half-life 5 hours

➤ Recommendation
➤ SAFE to continue
HYDROXYCHLOROQUINE

➤ Did you know?
  ➤ Have been used in the past to prevent postoperative venous thromboembolism
  ➤ Long half-life (40-50 days)

➤ Recommendation
  ➤ SAFE to continue
BIOLOGICS

- Becoming a concern in preoperative assessment
  - growing number of biologics
  - growing number of indications
  - growing number of patients facing surgery
  - but very limited data

- In general, long half-life
  - days… sometimes months…

- If urgent surgery, proceed
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment groups</th>
<th>Outcome studied</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawakami et al, 2010</td>
<td>retrospective case-control</td>
<td>Anti-TNF vs DMARDs</td>
<td>surgical site infection, DVT, disease flares</td>
<td>Anti-TNF more likely to cause SSI and DVT</td>
</tr>
<tr>
<td>Hirano et al, 2010</td>
<td>retrospective cohort</td>
<td>Anti-TNF vs DMARDs</td>
<td>wound healing, febrile episode, infections</td>
<td>No specific adverse effects</td>
</tr>
<tr>
<td>*den Broeder et al, 2007</td>
<td>retrospective parallel cohort</td>
<td>No anti-TNF vs Anti-TNF withheld vs continue</td>
<td>infection rates, wound healing</td>
<td>Anti-TNF not important risk factor</td>
</tr>
<tr>
<td>Ruyssen-Witrand et al, 2007</td>
<td>retrospective</td>
<td>Discontinuation of anti-TNF at various time before surgery</td>
<td>complication rates</td>
<td>No difference</td>
</tr>
<tr>
<td>Giles et al, 2006</td>
<td>retrospective</td>
<td>Anti-TNF vs no anti-TNF</td>
<td>serious postop infections</td>
<td>Significant association with anti-TNF and post-op infections</td>
</tr>
<tr>
<td>Talwalkar et al, 2005</td>
<td>retrospective</td>
<td>Continuous anti-TNF vs stopped before surgery</td>
<td>infectious complications</td>
<td>No difference</td>
</tr>
<tr>
<td>Wendling et al, 2005</td>
<td>retrospective</td>
<td>Continuous anti-TNF vs stopped before surgery</td>
<td>infections, diseases flares</td>
<td>No difference</td>
</tr>
<tr>
<td>Bibbo &amp; Goldberg, 2004</td>
<td>prospective</td>
<td>Anti-TNF vs DMARDs</td>
<td>infections, wound healing</td>
<td>No difference</td>
</tr>
</tbody>
</table>

Adapted from Akkara Veetil and Bongartz, Nature Rheumatology, 2012;8:32-41
Most data on anti-TNF agents

- retrospective
- varying definitions of exposure and outcomes
- mostly orthopedic surgeries
- underestimate risk of disease flares
  - problems with early mobilization

In Crohn’s disease, infliximab within 3 months of surgery associated with increase risk of postop sepsis, abcess and readmission

RECOMMENDATION FOR BIOLOGICS

➤ For anti-TNF agents, abatacept and tocilizumab
  ➤ 1 week to 2 months

➤ For rituximab
  ➤ 6 months, or longer until peripheral B cell count is normal

➤ According to surgical scenario
  ➤ holding agent for 2 half-lives if sterile environment (cataract)
  ➤ holding agent for 5 half-lives if septic environment (colon) or septic risk situation (joint prosthesis)

➤ Royal College of Nursing, 2012
# MEAN HALF-LIFES OF BIOLOGIC AGENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Half-Life</th>
<th>2 Half-Lifes</th>
<th>5 Half-Lifes</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept (anti-TNF)</td>
<td>4.3 days</td>
<td>8.6</td>
<td>21.5</td>
</tr>
<tr>
<td>adalimumab (anti-TNF)</td>
<td>14</td>
<td>28</td>
<td>70</td>
</tr>
<tr>
<td>infliximab (anti-TNF)</td>
<td>8-10</td>
<td>16-20</td>
<td>40-50</td>
</tr>
<tr>
<td>golimumab (anti-TNF)</td>
<td>12</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>certolizumab (anti-TNF)</td>
<td>14</td>
<td>28</td>
<td>70</td>
</tr>
<tr>
<td>rituximab (anti-CD20)</td>
<td>21</td>
<td>42</td>
<td>105</td>
</tr>
<tr>
<td>abatacept (selective T-cell costimul blocker)</td>
<td>13</td>
<td>26</td>
<td>65</td>
</tr>
<tr>
<td>tocilizumab (anti-IL-6)</td>
<td>13</td>
<td>26</td>
<td>65</td>
</tr>
<tr>
<td>anakinra (anti-IL-1)</td>
<td>6 hours</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>tofacitinib (janus ass. kinase inhibitor)</td>
<td>3 hours</td>
<td>6</td>
<td>15</td>
</tr>
</tbody>
</table>
RECOMMENDATION FROM CRA, 2012

- Biologic DMARD should be held prior to surgical procedures. The timing for withholding biologic DMARD should be based on the individual patient, the nature of the surgery, and the pharmacokinetic properties of the agent.

- Biologic DMARD may be restarted postoperatively if there is no evidence of infection and wound healing is satisfactory.

  - Level II (anti-TNF), IV, Strength C
RECOMMENDATION FROM OTHER SOCIETIES

➤ American College of Rheumatology
  ➤ Withhold for more than 1 week

➤ British Society of Rheumatology
  ➤ Withhold for 3 to 5 half-lifes
PREDNISONE

➤ One of the highest overall infection rates

➤ Bridging patients for which DMARDs and biologics withheld

➤ Prescribe to avoid adrenal gland insufficiency
  ➤ can occur with equivalent of prednisone 5 mg daily for 4 weeks or 20 mg daily for 5 days...

  ➤ ACTH stimulation test
QUESTION #4

➤ Would you recommend a steroid stress dose?

➤ 1. Yes, without a doubt
➤ 2. Not sure, most probably
➤ 3. Maybe
➤ 4. No, certainly not!
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PREDNISONE AND PREOPERATIVE STRESS DOSE

➤ evidence that usual dosage is enough
  ➤ 2 small, randomized, double-blind studies
  ➤ directionally appropriate increase in serum cortisol levels
    ➤ cortisol level lower
    ➤ hemodynamic status not affected

➤ Thomason et al, Journal of Clinical Periodontology, 1999;26:577-582
➤ Glowniak et al, Surgery, 1997;121:123-129
➤ Marik et al, Archives of Surgery, 2008;143:1222-1226
PREOPERATIVE STRESS DOSES

➤ Superficial procedures - usual dose, no stress dose

➤ Minor surgeries (inguinal hernia repair) - 25 mg hydrocortisone or 5 mg methylprednisolone or prednisone day of surgery, then usual dose

➤ Moderate surgeries (open cholecystectomy, hemicolecctomy) - 50-75 mg hydrocortisone or 10-15 mg methylprednisolone day of surgery then taper over 1-2 days to usual dose

➤ Major surgeries (cardiothoracic, Whipple, liver resection) - 50-100 mg hydrocortisone or 20-30 mg methylprednisolone on day of surgery then taper over 1-2 days to usual dose

➤ Adapted from Coursin et al, JAMA 2002;287:236-240
NSAIDS AND ASPIRIN

➤ NSAIDS

➤ reversible inhibition of COX-1

➤ hold for 4 to 5 half-lifes

➤ naproxen 12-17 hours

➤ indomethacin 7-8 hours

➤ diclofenac, ibuprofen 2 hours

➤ COX-2 and meloxicam probably safer regarding blood loss

➤ Aspirin to be held 7 days
RISK OF THROMBOSIS

➤ Presence of antiphospholipid syndrome (APS)
  ➤ surgery, infection and change in anticoagulation can trigger the catastrophic APS

➤ Assess the need for bridging
  ➤ LMWH
  ➤ do consider risk of bleeding
  ➤ resume anticoagulation postoperatively
QUESTION #5

➤ What am I missing?

➤ 1. Nothing
➤ 2. One thing, but what?
➤ 3. Everything!? 
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RISK OF CERVICAL SPINE INSTABILITY

- Anaesthesiologic considerations
  - Rheumatoid arthritis patients
    - atlantoaxial subluxation
    - 80% of patients do have cervical findings, 30% have unsteadiness, sometimes asymptomatic
  - Ankylosing spondylitis patients
    - at risk for cervical fracture with minor trauma
    - atlantoaxial subluxation
RECOMMENDATION

➤ Expert opinion

➤ Obtain flexion-extension cervical spine XRay if
  ➤ joint findings
  ➤ cervical pain or findings suggestive of compression (spasticity, spastic gait, ...)

![Image of a person with a highlighted neck area]
TAKE-HOME MESSAGES

➤ Patients with increased cardiovascular risk
  ➤ to consider as other traditional risk factors?…
➤ Generally safe to continue conventional DMARDs
➤ Biologics best withheld prior to surgery
  ➤ but lack of data…
➤ Lowest possible dose of steroid to be used perioperatively
  ➤ higher risk of infection!

➤ Highly individualized assessment
REFERENCES


➤ Akkara Veetil BM, Bongartz T, Perioperative Care for Patients with Rheumatic Diseases, Nature Review of Rheumatology, 2011;8:32-41


➤ Goodman, SM, Rheumatoid arthritis: Perioperative Management of Biologics and DMARDs, Seminars in Arthritis and Rheumatism, 2015;44:627-632