Perioperative Medicine: Management of rheumatologic agents

Divya Gollapudi, MD

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Medical Operative Consult Clinic
Harborview Medical Center
Your patient

Ms. L is a 55 year-old F w/ h/o RA who presents for pre-op evaluation for right hip arthroplasty for avascular necrosis of the right hip.

Current medications:
Methotrexate 20mg/week
Etanercept 50mg/week
Prednisone 10mg daily

She receives long steroid tapers or bursts 2 times per year.
DMARDs & anti-TNF agents

• Methotrexate
• TNF-blockers
• Hydroxychloroquine
• Azathioprine
• Sulfasalazine
• Leflunomide
• Cyclosporine
The Clinical Dilemma

Risks of Continuing Therapy

- Increased chance of infection?
- Compromised wound healing?

Risks of Discontinuing Therapy

- Increased chance of arthritis flare compromising post-operative recovery and rehabilitation?
Factors contributing to perioperative management

• Severity of underlying disease
• History of flares on & off drug
• Type of surgery
• Co-morbidities (↑ risk of infection)
• Patient preference
• Rheumatologist preference
Methotrexate (MTX)

- 388 patients randomized to continue or discontinue MTX
- ↑ surgical complications in patients who stopped MTX (15% vs. 2%)
- ↑ flares in patients who discontinued MTX (8% vs. 0%)
- Confirmed in other (small) studies

Methotrexate

• Continue through the perioperative period
• Consider lowering dose if > 20 mg/week
• Consider holding if hepatic or renal impairment
  – No evidence to support this practice
Tumor Necrosis Factor (TNF) blockers

- Infliximab (*Remicade*), etanercept (*Enbrel*), adalimumab (*Humira*), certolizumab pegol (*Cimzia*), golimumab (*Simponi*)
- Associated with ↑ risk of infection
  - OR 2.0 (NNH 59) for serious infection\(^1\)
- Perioperative data is limited and conflicting regarding:
  - Wound healing
  - Infections
  - Disease flares

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TNF-blocker recommendations

• In general, hold pre-operatively for approximately 2 half lives before major surgery
• Hold for 10-14 days post-op (or until wound healing)
• Consider continuation for minor surgery
• Discuss with rheumatologist and surgeon
TNF-blocker recommendations

<table>
<thead>
<tr>
<th></th>
<th>Pre-operative management</th>
<th>Post-operative management</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Rheumatology (2008, update 2012)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Hold for at least 1 wk before surgery and in proportion to the drug’s half-life</td>
<td>Hold for at least 1 wk after surgery</td>
</tr>
<tr>
<td>British Society of Rheumatology (2010)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Hold 3–5 times the half-life of the drug before surgery</td>
<td>Restart when adequate surgical wound healing and no evidence of infection</td>
</tr>
<tr>
<td>French Society of Rheumatology (2005)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Hold for 2 half-lives before surgeries in sterile environments and &gt;2 half-lives for septic environments&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Restart when adequate surgical wound healing and no evidence of infection</td>
</tr>
</tbody>
</table>

<sup>a</sup> Examples of surgeries with septic risk or in septic environments include removal of infected joint prosthesis or colectomy for sigmoiditis.

# Specific recommendations for biologic agents

<table>
<thead>
<tr>
<th>Biologic agent</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Hold for 2 wk</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Hold for 1 wk</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Hold for 6–8 wk</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Hold for 4 wk</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Hold for 4 wk</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Last dose 4 wk before surgery</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Last dose 3–6 mo before surgery</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Last dose 4 wk before surgery</td>
</tr>
</tbody>
</table>

Hydroxychloroquine

• 2 retrospective trials including hydrochloroquine – no associations with perioperative complications
• Half-life is 40-50 days
• Continue through perioperative period without interruption
Sulfasalazine

• No studies to guide perioperative management
• Half-life is 6-10 hours, with primarily renal elimination
• Given general risk of renal impairment, consider holding on AM of surgery
  • No evidence to support this practice
Azathioprine

• 2 retrospective trials including azathioprine – no associations with perioperative complications
• Continue through perioperative period without interruption
Leflunomide

• Conflicting evidence regarding wound healing in a few small trials\(^1\)
• Continue through operative period, unless anticipate large wounds or high infection risk
• Half-life is 2 weeks

Cyclosporine

• 5 small retrospective trials including cyclosporine – no association with perioperative complications

• Continue through the perioperative period

• May enhance effect of neuromuscular blocking agents

<table>
<thead>
<tr>
<th>Country</th>
<th>Study years</th>
<th>Condition</th>
<th>Duration of follow-up</th>
<th>No. receiving cyclosporin who had surgery</th>
<th>No. not receiving cyclosporin who had surgery</th>
<th>Total complications*</th>
<th>OR†</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>1991–1997</td>
<td>UC</td>
<td>Hospital stay</td>
<td>19</td>
<td>25</td>
<td>8 (57)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>USA</td>
<td>1997–1999</td>
<td>UC</td>
<td>30 days§</td>
<td>12</td>
<td>151</td>
<td>12 (63)</td>
<td>17 (68)</td>
</tr>
<tr>
<td>USA</td>
<td>1996–2002</td>
<td>UC</td>
<td>Hospital stay</td>
<td>18</td>
<td>12</td>
<td>4 (33)</td>
<td>7 (39)</td>
</tr>
</tbody>
</table>

# Perioperative management of nonbiologic DMARDs

<table>
<thead>
<tr>
<th>Non-biologic DMARD</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Continue through perioperative period</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Continue through perioperative period</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Continue through perioperative period; consider holding on AM of surgery given renal clearance</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Continue through perioperative period; consider holding for at least 2 wks if large surgical wounds anticipated</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Continue through perioperative period</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Continue through perioperative period</td>
</tr>
</tbody>
</table>
Ms. L

- Continue methotrexate through perioperative period
- Recommend holding entanercept for 1-2 weeks pre-operatively and 1-2 weeks post-operatively
- Discuss with prescribing provider!
Take Home Points

• Limited data suggests continuing methotrexate, sulfasalazine, azathioprine, and hydroxychloroquine, cyclosporine through perioperative period

• Hold TNF-blockers for at least 2 half-lives
References