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.

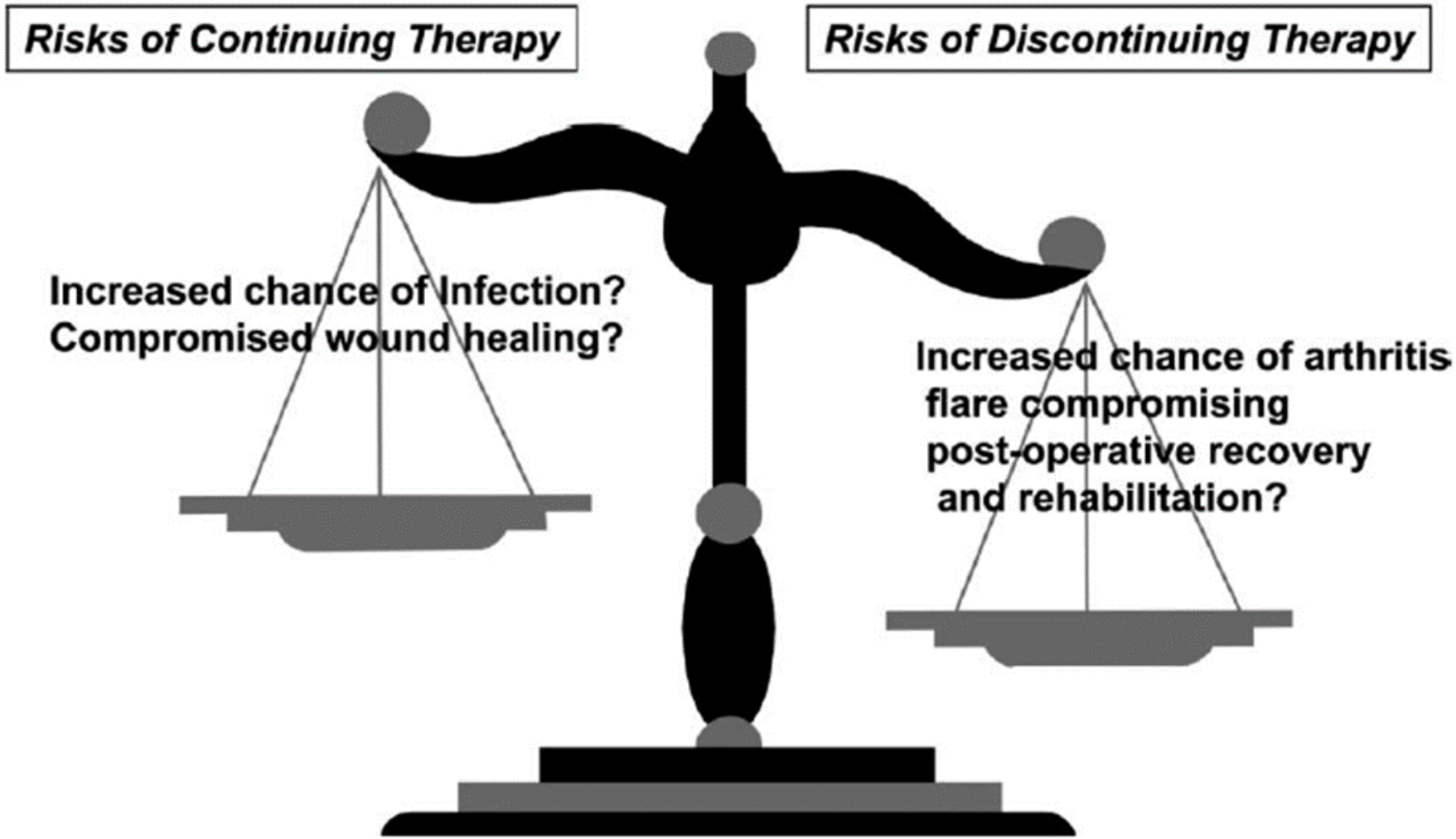
Current medications:
Methotrexate 20mg/week
Etanercept 50mg/week
Prednisone 10mg daily

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



Mushtaq S, et al. Am Journal of Therapeutics. 2011;18:426–434

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

Grant, P. Perioperatve Medicine Summit 2014.

Methotrexate (MTX)

Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery

D M Grennan, J Gray, J Loudon, S Fear

- 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

Grennan, et al.Ann Rheum Dis.2001;60:214-217

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

1. Bongartz T..JAMA;2006: 295(19):2275-85

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

	Pre-operative management	Post-operative management
American College of Rheumatology (2008, update 2012)[1]	Hold for at least 1 wk before surgery and in proportion to the drug's half-life	Hold for at least 1 wk after surgery
British Society of Rheumatology (2010)[2]	Hold 3–5 times the half-life of the drug before surgery	Restart when adequate surgical wound healing and no evidence of infection
French Society of Rheumatology (2005)[3]	Hold for 2 half-lives before surgeries in sterile environments and >2 half-lives for septic environments[a]	Restart when adequate surgical wound healing and no evidence of infection

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

1. Saag, et al. Arthritis & Rheumatism. 2008;59(6): 762–784
2. Ding T, et al. Rheumatology. 2010;49:2217–19
3. Pieringer H, et al. Semin Arthritis Rheum. 2007;36(5):278-86
4. Gollapudi D and Grant P. Hospital Medicine Clinics. 2016;5(2): 286-80

Specific recommendations for biologic agents

Biologic agent	Management
Adalimumab	Hold for 2 wk
Etanercept	Hold for 1 wk
Infliximab	Hold for 6–8 wk
Certolizumab pegol	Hold for 4 wk
Golimumab	Hold for 4 wk
Abatacept	Last dose 4 wk before surgery
Rituximab	Last dose 3–6 mo before surgery
Tocilizumab	Last dose 4 wk before surgery

1. Saag, et al. Arthritis & Rheumatism. 2008;59(6): 762–784
2. Ding T, et al. Rheumatology. 2010;49:2217–19
3. Pieringer H, et al. Semin Arthritis Rheum. 2007;36(5):278-86
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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

1. Goodman SM and Paget S.2012;38(4):747-59

Cyclosporine

- 5 small retrospective trials including cyclosporine – no association with perioperative complications[1]
- Continue through the perioperative period
- May enhance effect of neuromuscular blocking agents[2]

Country	Study years	Condition	Duration of follow-up	No. receiving cyclosporin who had surgery	No. not receiving cyclosporin who had surgery	Total complications*		
						Cyclosporin	No cyclosporin	OR†
USA	1993–1994	UC	Hospital stay	14	n.a.	8 (57)	n.a.	n.a.
Italy	1991–1996	UC	Hospital stay	25	n.a.	9 (36)	n.a.	n.a.
UK	1991–1997	UC	Hospital stay	19	25	12 (63)	17 (68)	0·8 (0·2, 2·8)‡
USA	1997–1999	UC	30 days§	12	151	4 (33)	49 (32·5)	1·0 (0·3, 3·6)
USA	1996–2002	UC	Hospital stay	18	12	7 (39)	4 (33)	n.a.

1. Subramanian V, et al. British Journal of Surgery. 2006;93:793–799 2. Kostopanagiotou, G et al. Anesth Analg 1999;89:613–22

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Perioperative management of nonbiologic DMARDs

Non-biologic DMARD	Management
Methotrexate	Continue through perioperative period
Hydroxychloroquine	Continue through perioperative period
Sulfasalazine	Continue through perioperative period; consider holding on AM of surgery given renal clearance
Leflunomide	Continue through perioperative period; consider holding for at least 2 wks if large surgical wounds anticipated
Azathioprine	Continue through perioperative period
Cyclosporine	Continue through perioperative period

Gollapudi D and Grant P. Hospital Medicine Clinics. 2016;5(2): 286-80

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

1. Grennan, et al. Methotrexate and early postoperative complications in patients with rheumatoid arthritis underoing elective orthopedic surgery. Ann Rheum Dis.2001;60:214-217
2. Goodman SM and Paget S. Perioperative drug safety in patients with rheumatoid arthritis. Rheum Dis Clin North Am. 2012;38(4):747-59
3. Saag, et al. American college of rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis & Rheumatism. 2008;59(6): 762–784
4. Ding T, et al. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. Rheumatology. 2010;49:2217–19
5. Mushtaq S, Goodman SM, Scanzello CR. Perioperative management of biologic agents used in treatment of rheumatoid arthritis. Am Journal of Therapeutics. 2011;18:426–434
6. Bongartz T. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA;2006: 295(19):2275-85
7. Pieringer H, Stuby U, Biesenbach G. Patients with rheumatoid arthritis undergoing surgery: how should we deal with antirheumatic treatment? Semin Arthritis Rheum. 2007;36(5):278-86.
8. Grant, P. Perioperative management of immunosuppressants and immunomodulators Perioperatve Medicine Summit 2014.
9. Subramanian V, et al. Systematic review of postoperative complications in patients with inflammatory bowel disease treated with immunomodulators. British Journal of Surgery. 2006;93:793–799
10. Kostopanagiotou G, et al. Anesthetic and perioperative management of adult transplant recipients in nontransplant surgery. Anesth Analg 1999;89:613–22
11. Gollapudi D and Grant P. Medication management for patients on rheumatologic agents or chronic steroids. Hospital Medicine Clinics. 2016;5(2): 286-80