2017 PERIOPERATIVE MEDICINE SYMPOSIUM

Peri-operative use of immunosuppression in rheumatology patients

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NEW ERA IN MUSCULOSKELETAL MEDICINE

- New drugs - “Biologics”, “JAK inhibitor”
- New perspective
- Better surgical techniques

FUNDAMENTAL PRINCIPLE OF PERIOPERATIVE DRUG MANAGEMENT

- Balance between concerns of surgeons and need for good control of disease so that the patient can rehabilitate successfully

- *Infection*
- *Wound healing*

- *Flare of disease*
- *Adrenal suppression*

CLASS OF DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDS)

	Generic	Brand
Synthetic DMARDs	Methotrexate	Methoblastin
	Hydroxychloroquine	Plaquenil
	Sulfasalazine	Salazopyrin
	Leflunomide	Arava

CLASS OF DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDS)

	Generic	Brand
Biologic DMARDs	Infliximab	Remicade
	Etanercept	Enbrel
	Adalimumab	Humira
	Golimumab	Simponi
	Certolizumab	Cimzia

CLASS OF DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDS)

	Generic	Brand
Biologic DMARDs	Tocilizumab	Actemra
	Abatacept	Orencia
	Ustekinumab	Stelara
	Secukinumab	Cosentyx
	Rituximab	Mabthera

CLINICAL VIGNETTES

CASE 1

- 65 year old with 5 year history of well controlled rheumatoid arthritis
- Elective R TKR for secondary osteoarthritis
- Other PHx: Hypertension, hypercholesterolemia, Stage 3 chronic renal failure (eGFR 45-50)
- Meds include MTX 15mg weekly, folate 5mg weekly, HCQ 200mg, PNL 5mg; atorvastatin 20mg, perindopril 5mg

CASE 1 PERIOPERATIVE DMARD MX

WHICH OF THE FOLLOWING OPTIONS IS THE MOST CORRECT?

1. Stop MTX/ HCQ for 2 weeks prior to surgery and recommence 6weeks postop.
2. Continue HCQ, stop MTX on the week of surgery and recommence postop provided no deterioration in renal function
3. Continue HCQ and MTX as per normal
4. Stop MTX/ HCQ for 2 weeks prior to surgery, and increase PNL to 10mg daily as well as hydrocortisone 50mg did IV for the first 5 days

CASE 2

- 65 year old with 20 year history of severe rheumatoid arthritis
- Elective R TKR for secondary osteoarthritis
- Other PHx: Hypertension, hypercholesterolemia, bronchiectasis (mild)
- Meds include abatacept 125mg weekly SC, MTX 20mg weekly, folate 5mg weekly, leflunomide 20mg daily, HCQ 200mg, PNL 10mg; atorvastatin 20mg, perindopril 5mg
- Previously failed Etanercept, Infliximab, adalimumab
- ESR35-40 CRP 20-30 (PBS submission baseline ESR 60 CRP 50, demonstration of response requires 20% improvement)

CASE 2 PERIOPERATIVE BDMARD MX

WHICH OF THE FOLLOWING OPTIONS IS THE MOST CORRECT?

1. Continue all DMARD and abatacept as per normal
2. In consultation with rheumatologist, withhold abatacept 2 weeks prior to surgery. Arranged scheduling of TKR at end of biologic assessment period.
3. Withhold all DMARD except for prednisolone 2 weeks prior to surgery, and increase prednisolone dose to control flare if necessary.
4. Likely adrenal suppressed due to long term steroid, IV hydrocortisone 100mg qid for the first 3 days while patient was monitored in HDU, then prednisone 25mg daily for 5 days.

LITERATURE REVIEW

- No good quality level A evidence but many retrospective observational studies can shed insights into reasons behind current available guidelines
- Also shared experience from other medical settings eg in patients with other autoimmune diseases

FACTORS RELATED TO INFECTION & SURGICAL OUTCOMES

Patient factors	Surgical factors	Medication factors
Age	Elective vs emergency	Types of DMARD
Co-morbidities	Duration/ complexity	Half life
Disease activity	Risk of contamination	Monotherapy vs combination therapy
Previous infection	Prosthesis	Timing to commencement of DMARD
Nutritional state	Indication for surgery (eg revision)	
Functional status		

INFECTION IN RA PATIENTS

- Infection rates are higher in RA patients, especially
  - Pulmonary infections
  - Septic arthritis
  - Skin or other soft tissue infections
- Increased susceptibility to infection due to:
  - Underlying immune effects of the disease itself
  - Use of corticosteroids and immunosuppressive therapies

SAFETY OF RA PATIENTS IN TERMS OF SURGICAL OUTCOMES

- Systematic review and meta-analysis comparing complications following joint arthroplasty in **RA vs OA** patients
  - Reports from 1990-2011
  - 5 studies compared rates of infection

Ravi et al. Arthritis Rheum 2012;64(12):3839

RAVI ET AL (2012) META-ANALYSIS

Included studies	RA patients	OA patients	Surgery	Results/ outcomes of interest (RA vs OA)
Jamsen (2009)	3040	35298	TKA	Adjusted HR 1.86 (1.31-2.63) for infection requiring revision
Bongartz (2008)	328 hip 239 knee	1:1	TKA/ THA	RR 4.8 (1.2- 1.9) for postop infection in TKA
Chesney (2008)	71	1235	TKA	RA infection rate 4.4% OA infection rate 1.7%
Wymenga (1992)	?	?	362 TKA/ 2651 THA	Septic arthritis (2.5% TKA, 0.64% THA) within 1y. RA is a risk factor
Bengston (1991)	4243	7534	4243	Deep infection in RA 4.4% cf OA 1.7%

WHAT ABOUT THE DRUGS?

- Synthetic DMARDs - methotrexate is best studied
- Biologic DMARDs - the collective class of TNF inhibitors is best studied
- Corticosteroids

METHOTREXATE

Table 2 | Studies of methotrexate use during the perioperative period

Study	Design	Patients (on methotrexate), *n*	Recommendation: withhold methotrexate before surgery?
Murata *et al.* (2006)[24]	Retrospective	124 (60)	No
Bibbo *et al.* (2003)[61]	Retrospective	104 (104)	No
Jain *et al.* (2002)[62]	Retrospective	80 (46)	No
Grennan *et al.* (2001)[23]	Prospective	388 (88)	No
Carpenter *et al.* (1996)[63]	Prospective	32 (13)	Yes
Escalante *et al.* (1995)[64]	Retrospective/ prospective	204 (?)	No
Kasdan *et al.* (1993)[65]	Retrospective	42 (15)	No
Sany *et al.* (1993)[66]	Prospective	64 (32)	No
Perhala *et al.* (1991)[67]	Retrospective	121 (60)	No
Bridges *et al.* (1991)[68]	Retrospective	38 (19)	Yes

Veetil et al. Nature Rev Rheum 2011;32-41

LARGEST STUDY - GRENNAN ET AL 2001

- Prospective study of elective orthopaedic surgery for RA patients (UK)
  - Three groups:

    A. Continue MTX (n=88)

    B. Withheld 2 weeks pre and postop (n=72)

    C. Never treated with MTX (n=228)

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

	Group A (Continue MTX) n=88	Group B (Temporary WH) n=72	Group C (Not on MTX) n=228
Mean disease duration	18	19	20
Baseline articular index	14	16.5	15
MTX dose	10 (2.5-25)	7.5 (2.5-20)	-
MTX duration	3 years	3 years	

INFECTION

- Adjusted for co-morbidities, other medication use (including prednisolone)
- Complications were defined as:
    - Wound morbidity (redness/ discharge)
    - Wound dehiscence
    - Systemic infection
    - Loosening of prosthesis
    - Revision within 1 year

A. Continue MTX
B. Withheld 2 weeks pre and postop
C. Never treated with MTX

Table 5 Incidence of infection/complications as defined in "Methods". Results are shown as No (%)

Group	*Rubor*	*Discharge*	*Systemic*	*Dehiscence*	*Complication*	*Total*
A (88)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	2 (2)
B (72)	4 (6)	4 (6)	0 (0)	1 (1)	2 (3)	11 (15)
C (228)	9 (4)	10 (4)	2 (1)	2 (1)	1 (0.4)	24 (10.5)

Table 6 Logistic regression analysis of all patients studied

Intercurrent disease	*p Value*	*Odds ratio*	*95% Confidence interval*
Diabetes	0.005	4.34	1.57 to 11.97
Hypertension	0.03	3.04	1.14 to 8.10
Osteoporosis	0.0001	9.51	3.01 to 30.06
Bronchiectasis/psoriasis/diverticulitis	<0.0001	11.12	3.39 to 36.57
Asthma	0.02	3.20	1.20 to 8.57
Heart condition	0.004	6.97	1.87 to 25.95
Treatment			
Penicillamine	0.05	2.64	1.00 to 6.94
Gold	0.56	1.46	0.41 to 5.17
Azathioprine	0.6	1.28	0.51 to 3.24
Indometacin	0.05	2.64	1.00 to 6.94
Cyclosporin	<0.0001	33.78	6.54 to 17.44
Hydroxychloroquine	0.02	4.61	1.35 to 15.77
Chloroquine	0.003	30.88	3.13 to 305.08
Sulfasalazine	0.17	2.04	0.73 to 5.69
Diclofenac	0.3	1.64	0.64 to 4.20
Prednisolone*	<0.0001	21.13	5.00 to 89.22
Leg surgery	0.05	0.489	0.24 to 1.00
Arm surgery	<0.0001	0.15	0.06 to 0.37
Methotrexate	0.35	1.12	0.34 to 1.40
Flare up	0.1	0.18	0.02 to 1.37
Articular index	0.22	0.98	0.94 to 1.01
HAQ†	0.15	1.58	0.84 to 2.99

*Range of daily dose of prednisolone from 1 mg to 27 mg (mean dose 5.9 mg).
†HAQ = Health Assessment Quuestionnaire.

NO INCREASE IN INFECTION OR WOUND HEALING COMPLICATIONS IN PATIENTS WHO CONTINUED MTX THERAPY

- Risk factors such as concomitant diabetes or steroid treatment seems to be much more important
- Risk of flare 8% in those who discontinued MTX 2 weeks before surgery

ANTI-TNF INHIBITORS - INCONSISTENT FINDINGS

Table 3 | Studies of TNF blockers in the perioperative period

Study	Design	Treatment groups	Outcome studied	Recommendation
Kawakami *et al.* (2010)[26]	Retrospective case–control study	Anti-TNF vs DMARDs	Surgical site infections, DVT, disease flares	Anti-TNF agents more likely to cause SSI and DVT in patients with RA undergoing orthopedic surgery
Hirano *et al.* (2010)[69]	Retrospective cohort study	Anti-TNF vs DMARDs	Wound healing, febrile episodes, infections	No specific adverse effects on surgical wounds after orthopedic operations; might improve hemoglobin levels
den Broeder *et al.* (2007)[25]	Retrospective parallel cohort study	No anti-TNF vs anti-TNF withheld before surgery vs continuous anti-TNF	Infection rates, wound healing	Perioperative use of anti-TNF agents not an important risk factor for SSI
Ruyssen-Witrand *et al.* (2007)[28]	Retrospective	Discontinuation of anti-TNF at various times before surgery	Complication rates	No difference between patients who discontinued anti-TNF treatment >5 half lives before surgery and those who either discontinued nearer to surgery or did not stop treatment at all
Giles *et al.* (2006)[27]	Retrospective	Anti-TNF vs no anti-TNF	Serious postoperative infections	Significant association between use of anti-TNF agents and postoperative infections
Talwalkar *et al.* (2005)[70]	Retrospective	Continuous anti-TNF vs anti-TNF stopped before surgery	Infections, complications	No evidence that use or stoppage of anti-TNF agents increases the risk of infection or complications
Wendling *et al.* (2005)[71]	Retrospective	Continuous anti-TNF vs anti-TNF stopped before surgery	Infections, disease flares	No increase in adverse events associated with continuous anti-TNF treatment
Bibbo & Goldberg (2004)[72]	Prospective	Anti-TNF vs DMARDs	Infections, wound healing	No difference in wound healing or risk of infection

Abbreviations: DVT, deep venous thrombosis; RA, rheumatoid arthritis; SSI, surgical site infection; TNF, tumor necrosis factor.

Veetil et al. Nature Rev Rheum 2011;32-41

BIOLOGIC DMARDS

- Studies have exclusively focussed on TNF inhibitors
- Conflicting conclusions from the limited, generally low quality studies
    - Retrospective
    - Varying definitions of exposure and outcomes
        - Orthopaedic surgeries only
- Outside peri-operative setting, the increased infection risk in TNF inhibitors is well established
- No definite conclusion can be drawn

LATEST GUIDELINE - ACR/AAHKS COLLABORATION

DMARDs: CONTINUE these medications through surgery.	**Dosing Interval**	**Continue/Withhold**
Methotrexate	Weekly	Continue
Sulfasalazine	Once or twice daily	Continue
Hydroxychloroquine	Once or twice daily	Continue
Leflunomide (Arava)	Daily	Continue
Doxycycline	Daily	Continue

Goodman et al. Arthritis Rheum 2017;69(8) 1538-1551
Goodman et al. J Arthroplasty 2017;32(9)2628-2638

BIOLOGIC AGENTS: STOP these medications prior to surgery and schedule surgery at the end of the dosing cycle. RESUME medications at minimum 14 days after surgery in the absence of wound healing problems, surgical site infection, or systemic infection.	**Dosing Interval**	**Schedule Surgery (relative to last biologic agent dose administered) during**
Adalimumab (Humira)	Weekly or every 2 weeks	Week 2 or 3
Etanercept (Enbrel)	Weekly or twice weekly	Week 2
Golimumab (Simponi)	Every 4 weeks (SQ) or every 8 weeks (IV)	Week 5 Week 9
Infliximab (Remicade)	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Abatacept (Orencia)	Monthly (IV) or weekly (SQ)	Week 5 Week 2
Certolizumab (Cimzia)	Every 2 or 4 weeks	Week 3 or 5
Rituximab (Rituxan)	2 doses 2 weeks apart every 4-6 months	Month 7
Tocilizumab (Actemra)	Every week (SQ) or every 4 weeks (IV)	Week 2 Week 5
Anakinra (Kineret)	Daily	Day 2
Secukinumab (Cosentyx)	Every 4 weeks	Week 5
Ustekinumab (Stelara)	Every 12 weeks	Week 13
Belimumab (Benlysta)	Every 4 weeks	Week 5
Tofacitinib (Xeljanz): STOP this medication 7 days prior to surgery.	Daily or twice daily	7 days after last dose

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PREDNISOLONE

- Associated with one of the highest overall infection rates, exceeding the risks associated with most conventional DMARDs and biologics
- Inappropriate use of corticosteroid is often multi-factorial
- Concerns regarding adrenal suppression in the peri-operative setting

Smitten et al. J Rheum 2008;35:387-393

ADRENAL SUPPRESSION

- Dependent on dose of steroid and duration - in susceptible patients, may only require as little as 5mg daily after just 12 weeks of therapy!
- Dependent on type of surgery
- A simple short synacthen test can help clarify whether patient needs peri-operative corticosteroid supplementation:
  - Basal, 30min, 60min serum cortisol after synthetic ACTH (Synacthen) 250mcg
  - Any level >550nmol/L indicates normal adrenal response

Kirwan et al. Arthritis Rheum 2006;54:1415-1421
Veetil et al. Nature Rev Rheum 2011;32-41

ADRENAL SUPPLEMENTATION THERAPY

Table 1 | Guidelines for adrenal supplementation therapy[19]

Medical or surgical stress	Corticosteroid dosage
Minor	
Inguinal hernia repair Colonoscopy Mild febrile illness Mild–moderate nausea/vomiting Gastroenteritis	25 mg hydrocortisone or 5 mg methylprednisolone intravenous on day of procedure only
Moderate	
Open cholecystectomy Hemicolectomy Significant febrile illness Pneumonia Severe gastroenteritis	50–75 mg hydrocortisone or 10–15 mg methylprednisolone intravenous on day of procedure; taper quickly over 1–2 days to usual dose
Severe	
Major cardiothoracic surgery Whipple procedure Liver resection Pancreatitis	100–150 mg hydrocortisone or 20–30 mg methylprednisolone intravenous on day of procedure; taper quickly over 1–2 days to usual dose
Critically ill	
Sepsis-induced hypotension or shock	50–100 mg hydrocortisone intravenous every 6–8 h or 0.18 mg/kg/h as a continuous infusion plus 50 μg per day fludrocortisone until shock resolved; may take several days to a week or more, then gradually taper, following vital signs and serum sodium

NOT IN SCOPE TODAY

- Other medication use in the perioperative period:
  - NSAID
  - Non-RA patients eg azathioprine or mycophenolate in SLE
- Other peri-operative consideration in rheumatology patients:
  - VTE assessment eg antiphospholipid syndrome
  - Issues relating to spinal anatomy
  - Cardiovascular risk assessment

CASE 1

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CASE 2

- 65 year old with 20 year history of severe rheumatoid arthritis
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CASE 2 PERIOPERATIVE BDMARD MX

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CONCLUSIONS

- Despite relatively poor level of evidence, there is a general consensus for recommendations in relation to peri-operative use of immunosuppression for patients with rheumatic diseases.
- Most evidence suggests a neutral effect of conventional DMARDs in the peri-operative period, with no need to discontinue them prior to surgery.
- With the novel biological DMARDs, close communication with the treating rheumatologist to discuss the timing to withhold and restart immunosuppression will ensure the best outcome for the patient.
- Minimising peri-operative steroid use is likely going to have a larger benefit in preventing peri-operative complication in patients