Troubleshooting Biologics in Rheumatic Disease 2022: Safety Issues for Primary Care

Mcgill Family Med Review Course
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Disclosures:
Advisory boards, speaker, clinical trials.....

- Amgen
- Merck
- Pfizer
- Novartis
- BMS
- UCB
- Roche
- Abbvie
- Lilly
- Janssen

Objectives

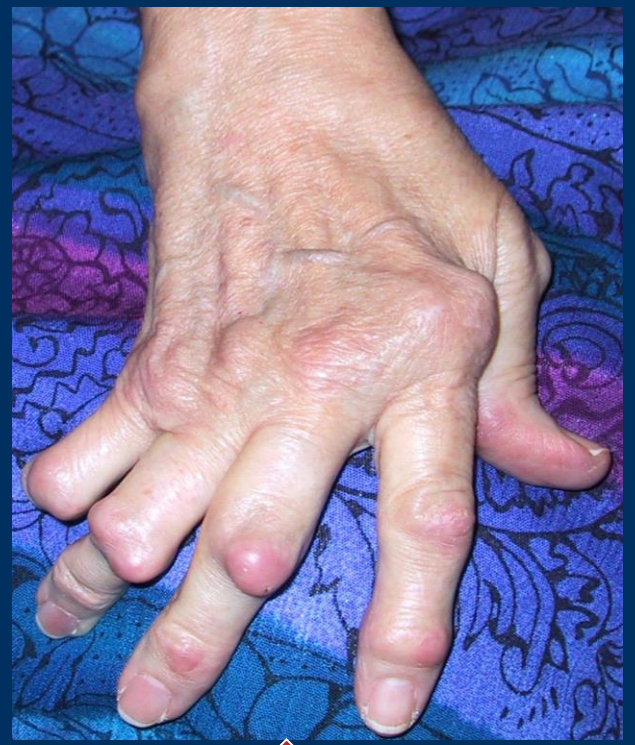
1. To review indications and rationale for using biological agents in Rheumatic inflammatory disorders.
2. To be aware of potential complications of Biologic drugs.
3. To improve comfort and skill level in recognizing special situations that may arise when using these agents.
4. To apply this knowledge to patients that are seen in daily practice who are using these medications.

RA joint deformities: various stages

Early RA

Intermediate RA

Severe RA



How did we get here?
Could it have been avoided?

Courtesy of J. Cush, 2002.

Prevention of Early Damage Preserves Function

Biologics have revolutionized the treatment of inflammatory arthritis:

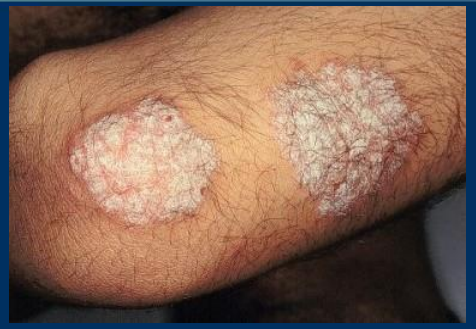
Compared to traditional DMARDS –>

- Reduced pain, joint swelling, and stiffness
- Improved function, work productivity
- Reduced radiographic destruction
- Reduced cardiovascular events
- Reduced mortality
- Higher remission rates

**All Biologics appear to be more effective when used in combination with Methotrexate

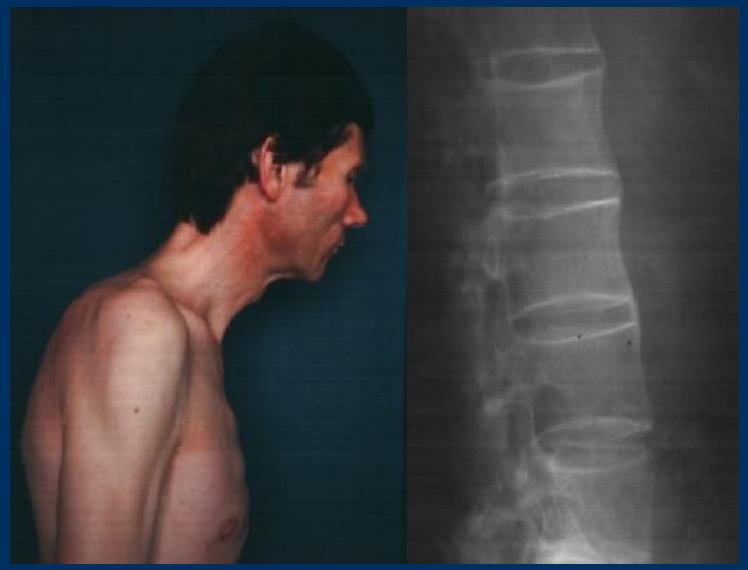
Biologics in Inflammatory Rheumatic Disease: Indications in Canada

Rheumatoid Arthritis (RA, JIA):

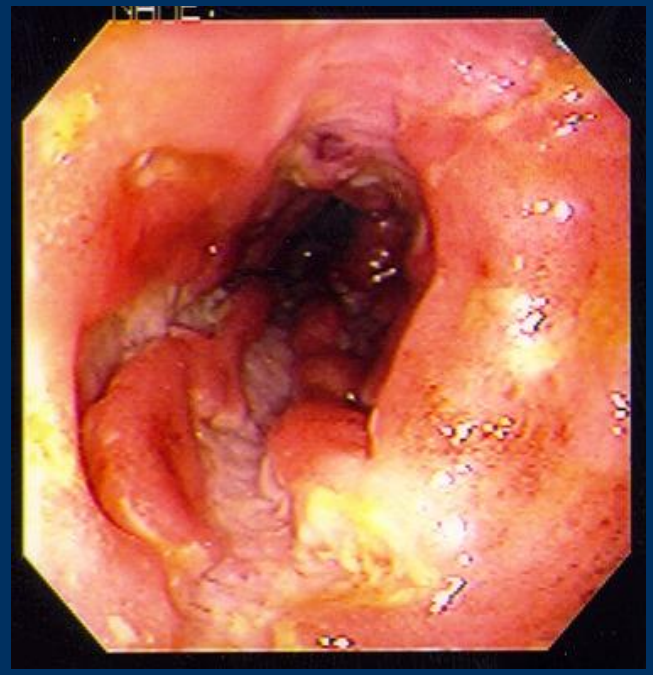


Psoriatic Arthritis (PsA)
& Psoriasis (PsO)

Ankylosing Spondylitis (AS):



Inflammatory Bowel disease: IBD



Anti-TNF Biologic Agents: There are 5

	Enbrel (Etanercept)	**Humira** (Adalimumab)	**Remicade** (Infliximab)	**Simponi** (Golimumab)	**Cimzia** (Certolizumab)
MOA	TNF receptor antagonist	mAb (human)	mAb (chimeric)	mAb	mAb (pegylated)
T 1/2	4-5 days	12-14 days	8-9.5 days	14 days	14 days
Route of Admin.	SC	SC	IV	SC/IV	SC
Dose/ Frequency	50 mg qw 25 mg biw	40 mg q2wks	3-10 mg/kg q8wks	50 mg Q4wks, IV q8wks	200 mg q2w 400 mg q4w
RAMQ (med d'exception)	Yes	Yes	Yes	Yes	Yes
Indications	RA, PsA, AS	RA,PsA,AS Uveitis,	RA, PsA, AS, Crohns	RA, PsA, AS	RA,PsA,AS (IBD in USA)

Non Anti-TNF Biologic Agents

	Orencia (Abatacept)	Rituxan (Rituximab)	Actemra (Tocilizumab)	Kineret (Anakinra)
MOA	Co-Stimulation T cell	Anti-CD20 B cell	Anti-IL6	IL-1 Ra
T 1/2	16.5 days	22 days	6 days	4-6 hrs
Route of Admin.	IV	IV	IV SC	SC
Dose/ Frequency	500-1000 mg q4w	1000mg q6m	8 mg/kg q4w	100 mg daily
RAMQ (medi d'exception)	Yes	Yes	Yes (for IV)	Yes
Indications	RA	RA, Lymphoma	RA, GCA	RA

Other Non Anti-TNF "Advanced" Therapies:

Stelara (Ustekinimab): IL-12/23 inhibitor (PsA, IBD)

Cosentyx (Secukinimab): IL-17 inhibitor (PsA, AS)
Taltz (Ixekizumab): IL-17 inhibitor -(PsA, AS)

Tremfya (Guselkumab): IL-23 inhibitor (PsA)
Skyrizi (Rizankizumab): IL-23 inhibitor (PsA)

JAK inhibitors: Xeljanz(Tofacitinib) - RA,PsA
Olumiant(Baricitinib)-RA
Upadicitinib(Rinvoq)-RA, PsA

Otezla(Apremilast): PDE4 inhibitor- (PsA)

Biosimilars

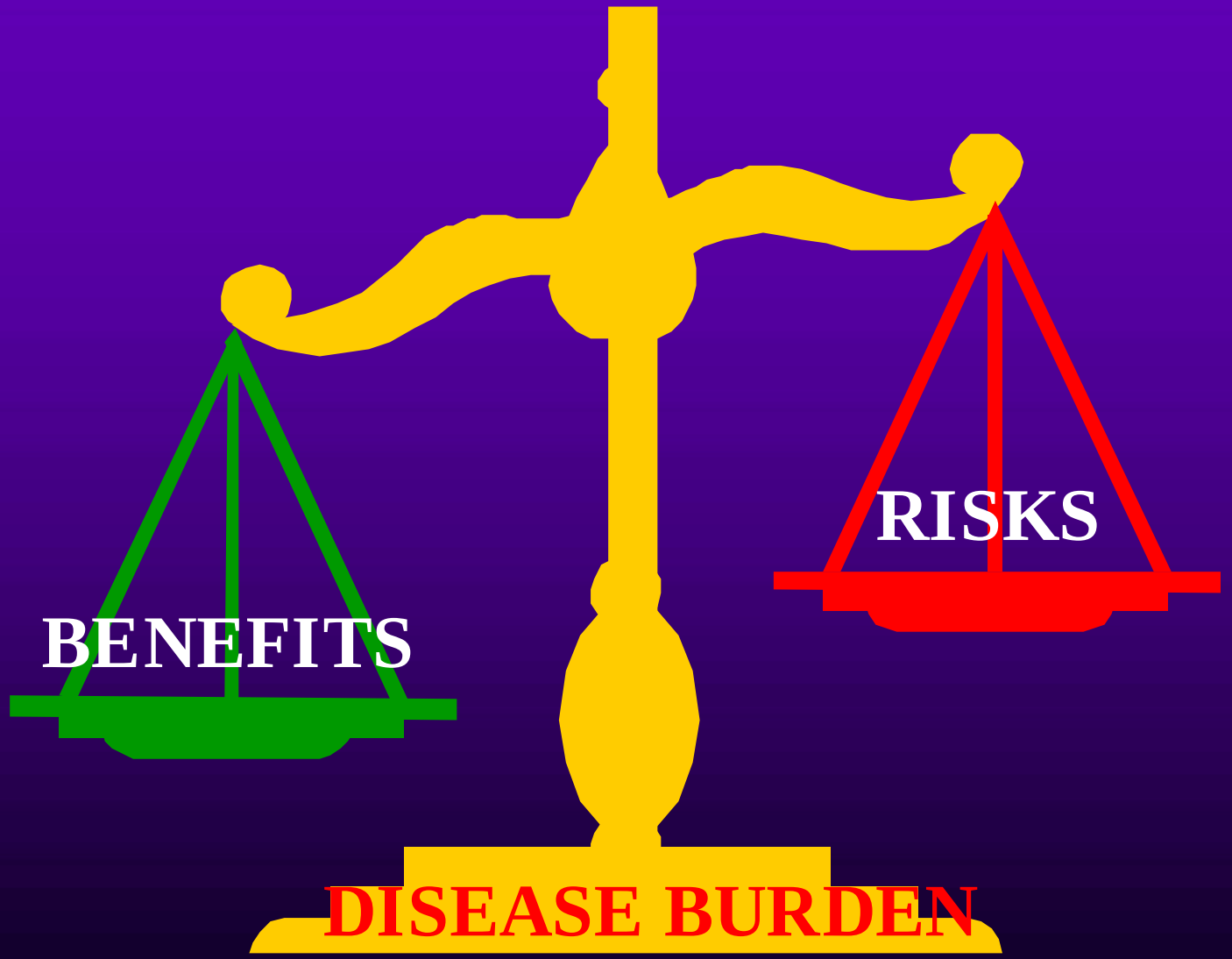
We Also Have “Biosimilars” :

Etanercept
Adalimumab
Infliximab
Rituximab

with more to come…..

Cost is 30-40% lower, otherwise they are “similar”
RAMQ has mandated these as 1st choice when available

I SHALL DO NO HARM….



Practical Safety Considerations with Biologics

- Infections (serious , opportunistic , TB)
- Malignancies
- Vaccinations
- Pregnancy
- Pre and Peri-op management

- CHF
- Demyelination
- Autoantibodies
- Injection/infusion reactions

Mini Case 1: Polling Question

- 61 year old male with RA , Tx with Adalimumab, MTX, Diclofenac. Presents to ER with cellulitus left leg, WBC 12.2, Temp 38. He is due for Adalimumab SC injection in 2 days.

  What should you do?

1. Start Ab's and tell him to take his Adalimumab as usual.
2. Don't give Ab's – they interact adversely with Adalimumab.
3. Start Ab's and tell him to hold Adalimumab until infection is clear and he is off antibiotics
4. Advise to stop Adalimumab permanently since he has demonstrated an increased infection risk.

Serious Infections

Predictors and Risk of Infection in RA

- Relative Risk compared to general population:1.9 (1.7-2.1)
- Best predictors:
  - RA severity / disease activity
  - Age
  - Corticosteroid therapy
  - Comorbid diseases: CVD, CHF, CRF, DM, lung disease
  - Skin infection
  - Joint surgery
- Contributory role of DMARDs not clearly defined

Moreland et al. *J Rheum* 2001;28:1238-44.

Serious Infections Rates by Anti-TNF-α Drug vs DMARD in RA Patients: BSR Biologics Registry

	DMARD n = 1354	ETN n = 3596	IFX n = 2878	ADA n = 1190
Exposure (PYs)	1352	4075	4618	1175
No. of infections	56	209	255	61
Rate of infections per 100 PYs (95% CI)	4.14 (3.14–5.35)	5.13 (4.47–5.85)	5.52 (4.88–6.22)	5.19 (3.99–6.62)
Adjusted IRR* (95% CI)	Referent	0.97 (0.63–1.50)	1.04 (0.68–1.61)	1.07 (0.67–1.72)

BSR = British Society of Rheumatology, IRR = incidence rate ratio; PY, person-years.
*Adjusted for age, sex, disease severity, comorbidity, extra-articular manifestations, steroid use, and smoking.

- **Crude rates of serious infections were similar for different anti-TNF-α drugs irrespective of drug half-life**
- **Compared with the DMARD-treated cohort, there was no increased risk of all-site serious infection for any of the 3 drugs(except maybe for skin and soft tissue)**

Dixon WG, et al. *Arthritis Rheum.* 2006;54:2368-2376.

Infections and Biologics: Summary Points

- All biologics have warnings about serious infections in product monograph
- Administration of any of the advanced therapies should be discontinued if the patient develops serious infection or sepsis and should not be initiated in patients with active infection
- Education of Pts. and MD’s is key

Recommended management of biologics in infection

- Simple upper respiratory tract viral infections:
  - No modification of treatment
- More severe viral infection (influenza, herpes zoster…) or severe bacterial infection (fever, bacteremia, systemic infection, recurrent infection…) :
  - Anti-TNF therapy should be temporarily discontinued
  - Appropriate antibiotic or antiviral therapy
  - Resumption of anti-TNF after resolution of the infection

Taylor PC. Presented at ACR Clinical Symposium: November 2007

Mini Case 2: Polling Question

- 62 yo male, just started Golimumab 10 weeks ago for his RA. He heard about the new Shingrix vaccine and asks if he should get it.

  What do you advise?

1. Wait till he is on a stable dose of GoI for at least 3 months and then can receive the vaccine
2. No point to give now since the biologic drug will suppress his ability to respond to the vaccine
3. Do not give- it is a live vaccine and so is contraindicated
4. Give Shingrix – but hold Biologic for 2-4 weeks

Avoid Live Vaccines

- BCG
- Polio
- Measles
- Mumps
- Rubella
- MMR
- Varivax (varicella)
- Yellow Fever
- Zostavax(zoster)
- Flumist (inhaled influenza vaccine)

Box 1 Recommendations for vaccination in adult patients with AIRD treated with biologics

1. Thorough assessment of vaccination status before beginning treatment with a biologic agent;
2. Vaccination can be administered during therapy with anti-TNF agents, TCZ and ABA but ideally should be given before B cell depleting biologicals are prescribed; and in both cases with the disease stabilised.
3. Live attenuated vaccines should be avoided.
4. The influenza and pneumococcal vaccines are strongly recommended
5. Tetanus toxoid vaccination should be administered as in the general population, except if the patient has been treated with RTX within the last 24 weeks and is at high risk of developing tetanus, in which case passive immunisation with tetanus immunoglobulin is strongly advised.
6. There are no data to help advice about the use of HZV, HPV, hepatitis A and/or B, *Haemophilus influenzae* b, meningococcal vaccines and BCG.

ABA, abatacept; AIRD, autoimmune rheumatic diseases; HPV, human papillomavirus; RTX, rituximab; TNF, tumour necrosis factor.

Vaccines and biologics

Isabel Ferreira,[1] David Isenberg[2]

Ann Rheum Dis, May, 2014

Other Vaccination Considerations

- Shingrix- not live, need 2 injections
- Vaccinate even with live vaccines at time of scheduled biologic injection?
- “High dose” Flu vaccine vs. regular Fluvax for RA patients? (recent Mcgill study)- can be difficult to access in Quebec, so recommend at least the regular quad vaccine

What about the Covid Vaccine for Rheumatic Disease Patients?

- Recommend to give! Benefits outweigh the Risks
- No evidence of disease exacerbation
- Issue is uptake of the vaccine in immune suppressed people or on biologics

- British Society Rheumatology recommendations Feb, 2021:
  - Ideally vaccinate 2 weeks prior to starting Advanced therapies
  - MTX, Abatacept, Jak's: Hold for at least a week post vaccine
  - Rituximab: give vaccine roughly 4 weeks prior to next RTX infusion
  - Anti-TNF's- no need to modify

Mini Case 3: Polling Question

- 54 yo female with severe RA. Breast cancer diagnosed after 10 months on Etanercept (anti-TNF). Will need Radiotherapy and Chemotherapy. The biologic has “changed her life” w.r.t. pain and function and QOL.

  What will you recommend?

1. Never give a biologic to this patient again - too high risk
2. No clear evidence of biologic association with solid tumours, so can continue Tx without worry
3. Hold biologic while patient treated for cancer and plan to restart if patient in remission
4. Switch to a non anti-TNF Biologic agent and continue treating her

Malignancy

Risk of Malignancies in RA Patients compared to general population: A Systematic Lit. Review

	SIR	95% CI
Total malignancy	1.05	1.01 to 1.09
Lymphoma	2.08	1.80 to 2.39
Lung	1.63	1.43 to 1.87
Colorectal	0.77	0.65 to 0.90
Breast	0.84	0.79 to 0.90

Smitten AL et al. Arthritis Res Ther 2008;10:R45.

TNF Inhibitors and Risk of Malignancy

US National Data Bank for Rheumatic Diseases[1]

- Biologic-treated patients (n = 13,001)
- Overall cancer risk was similar to general population (SIR = 1.0), but biologics were associated with increased skin cancer risk (melanoma and non-melanoma)

SEER, Surveillance, Epidemiology, and End-Results: SIR, standardised incidence ratio; IRR, incidence risk ratio

[1]Wolfe F, Michaud K. *Arthritis Rheum* 2007;56(9):2886-95
[2]Greenberg J et al. ACR 2007, Abstract 282

Anti-TNFα Agents and Lymphoma Risk – National Data Base: USA

Treatment	Observed Cases	Expected Cases	SIR (95% CI)
All treatments	79	45.0	1.8 (1.4–2.2)
ETN	10	4.0	2.5 (1.4–4.7)
IFX	27	13.1	2.1 (1.4–3.0)
ADA	2	0.8	2.4 (0.6–9.6)
All biologics	35	17.7	2.0 (1.4–2.8)
DMARDs (no biologics)	36	14.5	2.5 (1.8–3.5)

No increase in risk of lymphoma with anti-TNFα therapy, MTX or combination of both when controlling for disease activity (entry HAQ, number of prior DMARDs and use of prednisone).

Wolfe F. and Michaud K. EULAR 2006, Abstract SAT 0204.

Malignancies and Biologics: summary statements

- Risk of solid tumours does not appear to be increased by Biologic meds
- Lymphoma increased, but registry data suggest that it is the disease itself and not the treatment that confers the increased risk
- Skin cancer (Melanoma and NMSC) increased with Biologics
- No clear consensus , but in the context of cancer , need to have a risk/benefit discussion on a case by case basis to decide on Tx
- RTX may be best choice for biologic Tx if previous cancer
- JAK inhibitors - Oral Surveillance Study: Increased malignancy and CVS events with tofacitinib in an “at risk” population. Is this a class effect??

Mini Case 4: Polling Question

- 28 yo woman with AS, on adalimumab (anti- TNF). AS much better and now feels well enough to consider family planning.

  How should you counsel her?

1. Too risky for an AS flare during pregnancy, so pregnancy not advisable
2. Hold adalimumab for 3 months, then proceed with family planning
3. Continue adalimumab until she confirms she is pregnant and then stop
4. Continue adalimumab throughout pregnancy- no known pregnancy risk

Pregnancy Considerations- A Risk/Benefit Dilemma

- Effect of disease on pregnancy
  - Evidence of poorer outcomes and increased complications (low birth weight, HTN, miscarriage) in IBD, PsO, RA if disease active in pregnancy
  - AGA recommends disease should be in remission prior to conception and to maintain remission throughout
- Effect of drugs on the pregnancy

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Steroids In Neuroendocrine Immunology and Therapy of Rheumatic Diseases I*

Safety issues of biologics in pregnant patients with rheumatic diseases

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Table 1. Published experience on human pregnancies exposed to different TNF-α inhibitors

TNF-α inhibitor type	Type of studies	Number of human pregnancies exposed	Median percentage of maternal to cord serum level	Effect on pregnancy/child
Infliximab: complete IgG1 antibody	Case reports, cohort studies, case-control, registry data	>1000	160	No increase in miscarriage or malformations; no malformation pattern detected
Etanercept: fusion protein with Fc part	Case reports, cohort studies, case-control, registry data	>500	6	No increase in miscarriage or malformations; no malformation pattern detected
Adalimumab: complete IgG1 antibody	Case reports, cohort studies, case-control	>300	179	No increase in miscarriage or malformations; no malformation pattern detected
Golimumab: complete IgG1 antibody	Registry data	40	not done	Data not conclusive
Certolizumab: pegylated Fab fragment	Registry data and case reports	139	3.9	No increase in miscarriage or malformations; no malformation pattern detected

Table 2. Biologics with no or anecdotal human pregnancy experience

Biologic type	Type of studies	Number of human pregnancies exposed	Effect on pregnancy/child
Rituximab: complete IgG1 antibody	Case reports, registry data	~200	Preconception and early first-trimester exposure: in a few studies, no harm to child detected; second- and third-trimester exposure: B cell depletion in child
Abatacept: fusion protein with Fc part	One case report	1	No conclusive human data
Tocilizumab: complete IgG1 antibody	Case reports (abstracts)	39	No conclusive human data
Anakinra: IL-1 receptor antagonist	Case reports	3	Animal data: no harm in offspring. No conclusive human data
Belimumab: complete IgG1 antibody	No published data	83 unpublished	Animal data: no harm in offspring. No conclusive human data

“Motherisk” Recommendations

- Limited studies on safety of medications used in RA
- Balance potential benefits/risk with potential risk associated with untreated moderate-severe RA
- Risk/benefit ratio will vary from case to case

sulfasalazine, azathioprine, antimalarials	cumulative data reassuring
biologics (adalimumab, anakinra, etanercept, infliximab, certolizumab) anti TNF Class B	do not appear likely to pose a major teratogenic risk

www.motherisk.org

Conclusions: Pregnancy

- More data accumulated over time are required to fully evaluate the safety of anti-TNF agents during pregnancy. Increased placental transport of IgG in 3rd trimester (not for certolizumab-pegol though)

  Current data suggest that risk of using anti-TNF's in pregnancy is small

- Non- anti-TNF Biologics not recommended

- Reasonable consensus is to stop biologics once pregnant. Continue during pregnancy only if benefits for a particular case outweigh the risks.

Mini Case 5: Polling Question

- Your patient, 37 yo elementary school teacher has RA. She is doing well on adalimumab (anti-TNF) essentially in remission with no swollen joints, CRP normal. She asks you to write a note to stay home from work since she has an autoimmune disease and is on a biologic. She is worried about her risk of Covid. Do you:

1. Refuse to write the note- life has to get back to normal
2. Write the note to stay home since you agree she is too high risk
3. Only write the note if she has active inflammation, or co-morbidities
4. Stop her biologic since she is doing well, and tell her to stay at work

Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study

Jose L Pablos [1,2] María Galindo,[1] Loreto Carmona,[3] Ana Lledó,[1] Miriam Retuerto [1] Ricardo Blanco [4] Miguel A Gonzalez-Gay [4] David Martinez-Lopez,[4] Isabel Castrejón,[5] José M Alvaro-Gracia [5] David Fernández Fernández [6] Antonio Mera-Varela [6] Sara Manrique-Arija [7] Natalia Mena Vázquez [7] Antonio Fernandez-Nebro [7] RIER Investigators Group

Conclusions:

- We found that severe COVID-19 occurred in 31.6% of the rheumatic and 28.1% of non-rheumatic cohorts.
- Having a connective tissue disease but not its therapy was significantly associated with severe COVID-19.
- Other known risk factors as ageing or male sex also apply to patients with rheumatic diseases.

Pablos JL, *et al*. *Ann Rheum Dis* 2020;**79**:1544–1549. doi:10.1136/annrheumdis-2020-218296

What does the Quebec Government say about this?

Centre intégré universitaire de santé et de services sociaux de l'Ouest-de-l'Île-de-Montréal

Québec

Subject: Request for recognition of a withdrawal for medical reasons in the COVID-19 pandemic situation.

- Person receiving high doses of corticosteroids in the presence of all of the following conditions:
  - The treatment is administered systemically (oral or intravenous);
  - The treatment is given for 2 weeks or more;
  - The dose is higher than 20 mg of prednisone per day or its equivalent.
- Person with an autoimmune disease who is receiving one of the following treatments:
  - Biological agents which are immunosuppressants or immunomodulators;
  - Treatment with azathioprine, mycophenolic acid derivatives, cyclosporine or tacrolimus or other high dose antimetabolites;
- Person with primary immunodeficiency, primarily of cellular immunity.

Mini Case 6: Polling Question

- 67 yo man on adalimumab(anti-TNF) for RA. Booked for a hip replacement (THR).

  How do you advise him to deal with the biologic drug?

1. Stop the drug at least 1-2 weeks prior to Sx (depending on T 1/2)
2. No need to stop – no evidence of increased infection risk for elective surgery
3. Time the biologic injection as close to the Sx as possible, since increased disease activity prior to Sx may actually increase the infection risk
4. Stop anti-TNF agent 3 months prior to elective surgery

Biologics in the peri-operative period in RA – theoretical considerations:

- TNF blockade may increase the risk of post-operative infection (by decreasing leucocyte trafficking and neutrophil recruitment)

- May also impair wound healing (by decreasing angiogenesis)

Arthritis Care & Research
Vol. 65, No. 12, December 2013, pp 2032–2040
DOI 10.1002/acr.22077

ORIGINAL ARTICLE

Infection Risk After Orthopedic Surgery in Patients With Inflammatory Rheumatic Diseases Treated With Immunosuppressive Drugs

CATRINA B. SCHERRER,[1] ANNE F. MANNION,[1] DIEGO KYBURZ,[2] MARKUS VOGT,[3] AND INÈS A. KRAMERS-DE QUERVAIN[1]

Table 4. Descriptive statistics and ORs from the multiple logistic regression with the degenerative/posttraumatic group as the reference, adjusted for the propensity score*

	Degenerative/ posttraumatic group	IRD without DMARDs†	IRD + conventional DMARD(s)†	IRD + TNFα inhibitor‡
Surgeries, no.	47,887	451	756	122
Infections, no. (%)	373 (0.8)	7 (1.6)	21 (2.8)	7 (5.7)
Adjusted OR (95% CI)	1.0 (reference)	1.60 (0.75–3.43)	3.41 (2.18–5.34)	6.90 (3.16–15.07)
P		0.222	< 0.001	< 0.001

* OR = odds ratio; IRD = inflammatory rheumatic disease; DMARDs = disease-modifying antirheumatic drugs; TNFα = tumor necrosis factor α; 95% CI = 95% confidence interval.
† Plus or minus corticosteroids.
‡ Plus or minus corticosteroids and/or conventional DMARD(s). For TNFα inhibitor therapy, only if the last dose was taken ≤3 administration intervals prior to surgery.

Highest risk if hold TNF drug less than 1 cycle of usual dosing

Conclusions: Safety Biologics

- Treatment of Inflammatory disease patients with Biologic therapy is generally safe and well tolerated
- Rare, important events have been seen with all TNF antagonists
  - Serious infections
  - TB and other opportunistic infections (more common with mAb's)
  - Lymphomas
  - Demyelinating events, CHF, Lupus-like reactions, Hepatic and Hematologic abnormalities
  - Don't use non-anti TNF biologics in pregnancy

- Screening for TB recommended in all patients
- Updated vaccinations recommended
- Vigilance required re: infectious and malignant complications
- Patient and physician education key

Thank You !