Biologic Update in Rheumatic Disease 2018: What the Primary Care Physician Needs to Know

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Disclosures:
Advisory boards, speaker, clinical trials.....

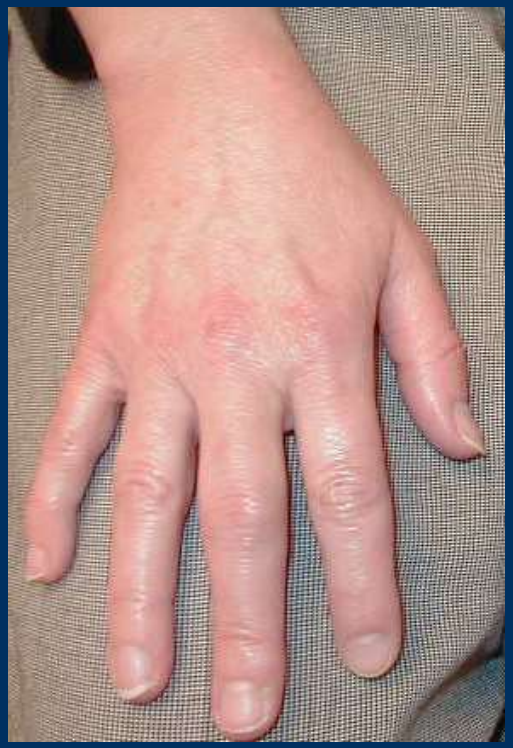
- Amgen
- Merck
- Pfizer
- Novartis
- BMS
- UCB
- Roche
- Abbvie
- Celgene
- Janssen

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

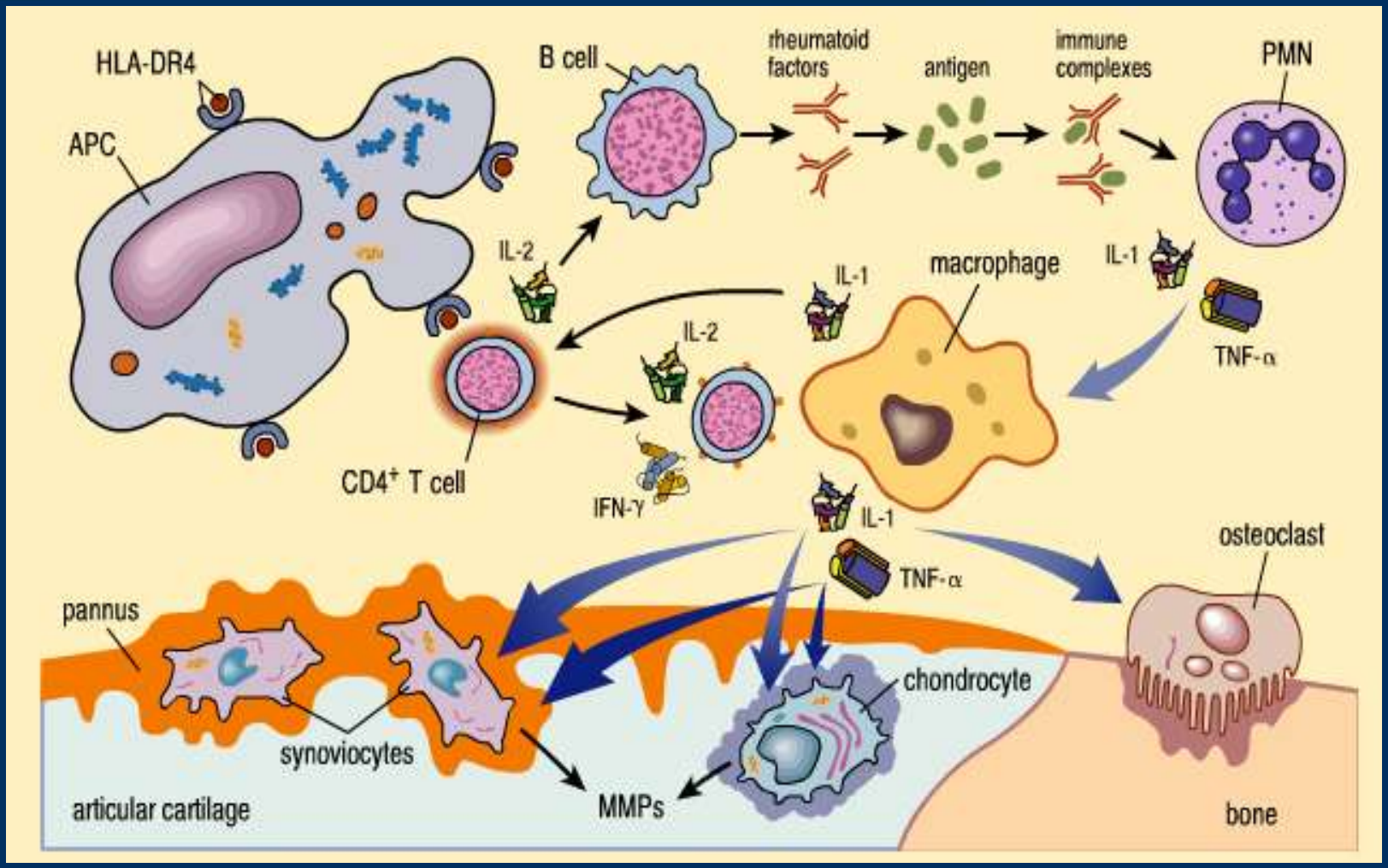
Severe RA

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

Courtesy of J. Cush, 2002.

Prevention of Early Damage Preserves Function

RA Pathophysiology:
Role of T-Cells, B-Cells, & Cytokines



B Haraoui E Keystone. *Mechanisms in Rheumatology* ©2001.

Biologics have revolutionized the treatment of inflammatory arthritis:

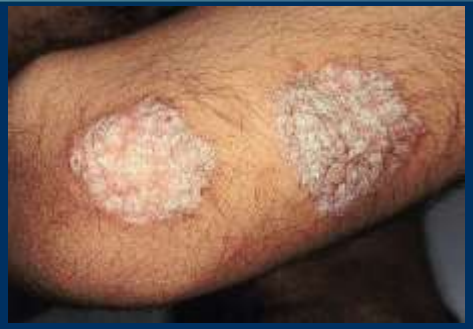
Compared to traditional DMARDS –>

- 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

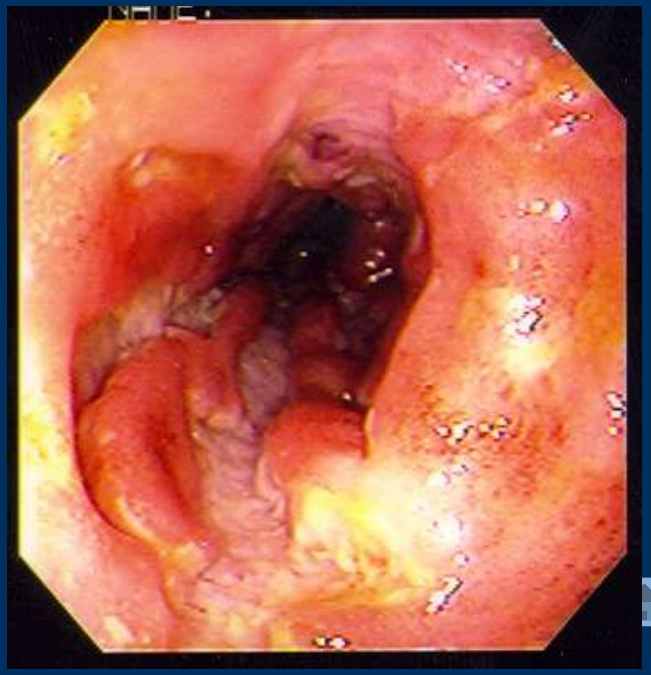
Biologics in Inflammatory Rheumatic Disease: Indications in Canada

Rheumatoid Arthritis (RA):

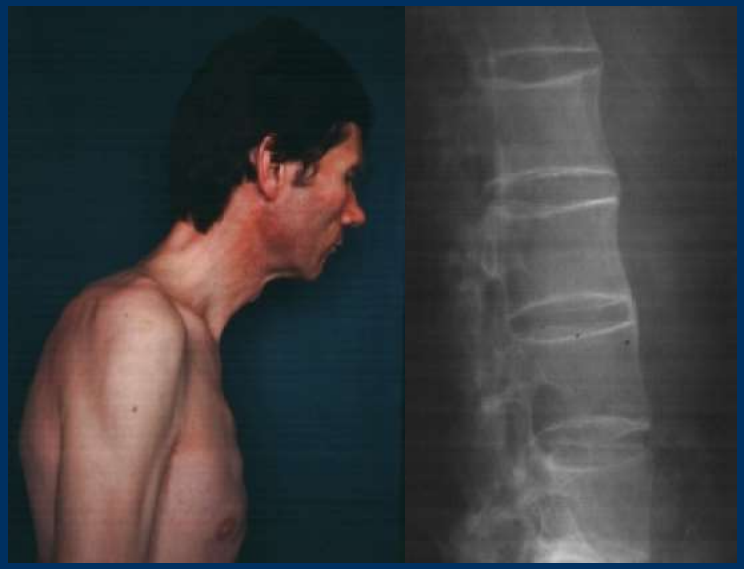


Psoriatic Arthritis (PsA)
& Psoriasis (PsO)

Inflammatory Bowel disease: IBD



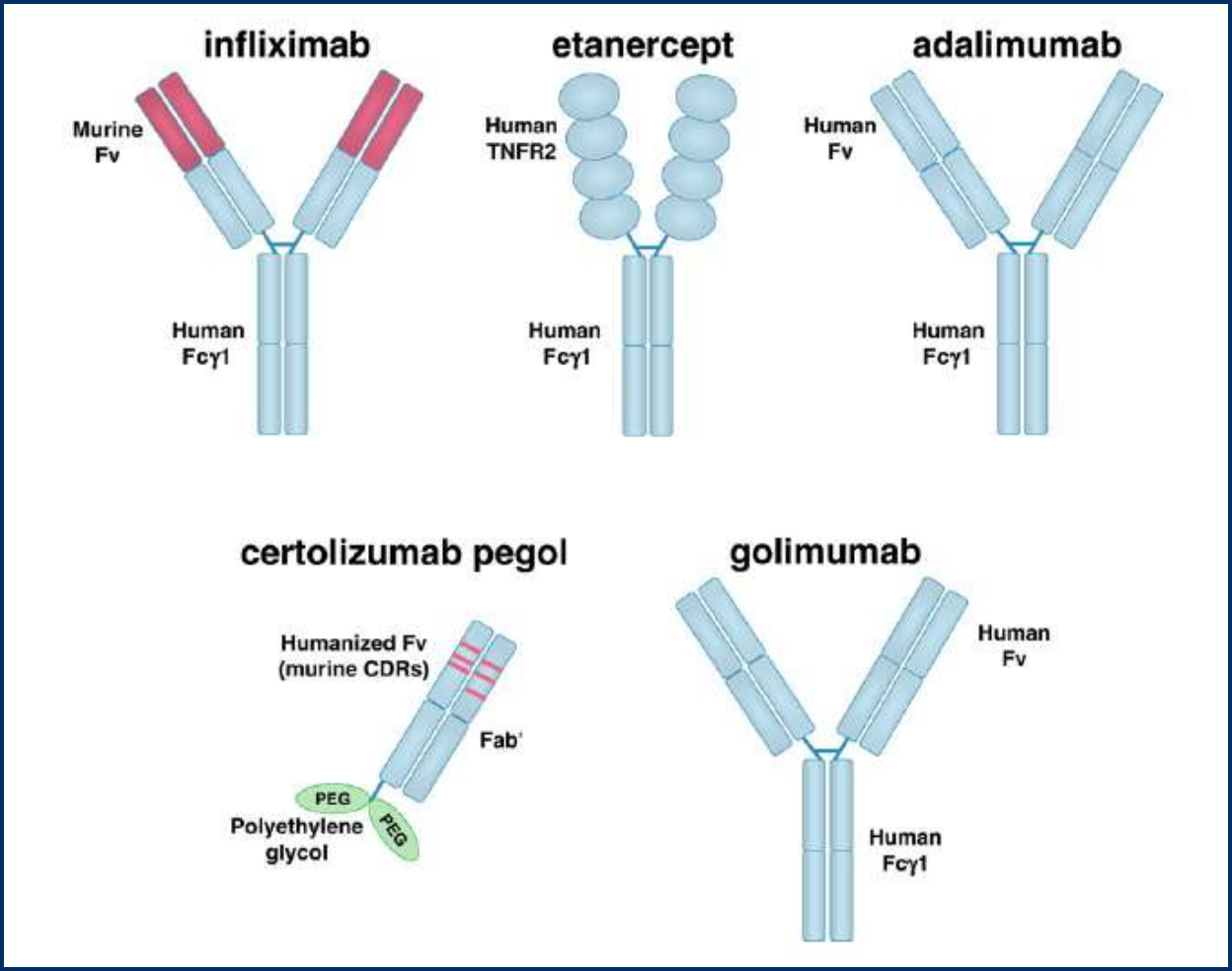
Ankylosing Spondylitis (AS):



Anti-TNF Biologic Agents

	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	3-5 mg/kg q8wks	50 mg q4wks	200 mg q2w 400 mg q4w
RAMQ (med d'exception)	Yes	Yes	Yes	Yes	Yes
Indications	RA, PsA, AS	RA, PsA, AS, Crohns	RA, PsA, AS, Crohns	RA, PsA, AS	RA,PsA,AS

Anti-TNFα Biologics for RA



Taken from Fig 4 – Tracey D, et al. Tumor necrosis factor antagonists mechanisms of action: A comprehensive review. Pharmacology & Therapeutics 117 (2008) 244–279.

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

Ustekinimab- for PsA (anti IL-12/23), Secukinimab- for PsA, AS (anti-- Il-17), New oral non- biologic JAK Inhibitor: Tofacitinib for RA

Other Non Anti-TNF “Advanced” Therapies:

Kevzara(Sarilumab): IL-6 inhibitor (RA)

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

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

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

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

Otezla(Apremilast): PDE4 inhibitor- (PsA)

RA Case:

- 37 yo female, RA for 4 years
- On MTX 25 mg/wk, Plaquenil 400mg/d, prednisone 7.5 mg/d, Ibuprofen 600 mg tid
- 12 swollen joints, CRP 22, HAQ score 1.8
- Erosions on xray , and even more detected on MRI

**This patient is an excellent candidate for addition of Biological agents

RAMQ Criteria Biologics: RA

- Active disease:
  - >8 swollen joints
  - HAQ >1
  - ↑CRP
  - Erosions on x-ray

  - Despite: >3 months of 2 DMARDS (1 of which being MTX >20mg)

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

- 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.
4. Advise to stop Adalimumab permanently since it has increased his infection risk.

Serious Infections

Predictors and Risk of Infection in RA

- Relative Risk 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: Anti-TNF Agents

- All TNF antagonists have warnings about serious infections in package insert
- Administration of any of the anti-TNF 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 anti-TNF 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

- 43 year old Asian male with PsA. On MTX, NPXN, HC cream, about to start Etanercept.

  Pre-TNF: CXR n, PPD pos. 7 mm, never received BCG.

  What would you do?

1. Go ahead with Tx – Etan not associated with TB compared to other anti-TNF agents (MAB's)
2. Tell patient he is too high risk for TB and so should never receive an anti-TNF.
3. Go ahead with Tx- PPD was <10 mm, and so considered negative.
4. Hold Tx temporarily, and give patient INH for 9 months.

Tuberculosis

Tuberculosis in RA

- 4 fold increase of TB incidence in RA
  - varies with geographic area

- General TB risk factors:
  - immunosuppression from medication
  - debilitation
  - aging population
  - migratory movements
  - immunocompromised states

Carmona, *J Rheum* 2003;30:1436-9

Tuberculosis (TB): Background

- Animal models[1]
  - TNF necessary for granuloma homeostasis
  - Inhibition of TNF associated with granuloma disruption

- In humans
  - Cases of TB have been seen in patients treated with all the TNF antagonists[2]
  - Commonly extra-pulmonary
  - Great majority of cases felt to represent reactivation
  - Risk factors include concomitant corticosteroids and diabetes
  - Patients should be screened for TB prior to beginning TNF antagonist therapy[3]

[1]Flynn, et al, *Ann Rev Imm,* 2001;19:93-121
[2]Keane, et al, NEJM, 2001;345:1098-1104
[3]Furst, et al, *Ann Rheum Dis,* 2002;61:(Suppl II):ii-ii7

TB: British Society of Rheumatology Biologics Register (BSRBR)

- **Numbers and rates of incidents tuberculosis, limited to first anti-TNF drug (F/U censored at date of starting second anti-TNF drug)**

Number of patients ever received drug	DMARD (n=3232)	All anti-TNF (n=10,712)	ETN (n=3913)	IFX (n=3295)	ADA (n=3504)
Actively receiving drug, person years (p-yrs)	7,345	23,286	10,111	7,459	5,716
Cases of TB	-	24	4	11	9
Rate/100,000 p-yrs (95% CI)	-	103 (66,153)	40 (11, 101)	147 (74, 264)	157 (72, 299)
IRR, adjusted for age, sex and entry year (95% CI)	-	-	Referent	3.7 (1.1, 12.7))	4.4 (1.3, 15.2)
Most recent drug exposure, person years (p-yrs)	7,345	27,624	11,926	8,963	6,735
Cases of TB	-	33	6	12	15
Rate /100,000 p-yrs (95% CI)	-	119 (82, 168)	50 (18, 110)	134 (69, 234)	223 (125, 367)
IRR, adjusted for age, sex and entry year (95% CI)	-	-	Referent	2.7 (0.9, 7.8)	4.4 (1.6 , 12.1)

Dixon WG et al. Ann Rheum Dis 2010;69:522-8.

Anti-TNF Agents and Opportunistic Infections

- Opportunistic infections are rare but have been observed in patients on biologic therapies
  - Bacterial, viral, and fungal infections, including histoplasmosis, listeriosis, *Pneumocystis carinii*, cytomegalovirus and herpes zoster[1-3]

- Risk may be reduced for etanercept vs anti-TNF monoclonal antibodies[1,3]

[1]Keystone E. *J Rheum.* 2005;32 (74):8-12.
[2]www.fda.gov/cder/drug/InfoSheets/HCP/TNF_blockersHCP.htm
[3]Strangfeld A et al. *JAMA* 2009;301:737-44
[3]Maury et al. *Arthritis Rheum* 2005: 52: S347

TB - the bottom line

- Exacerbation of latent TB more common with monoclonal TNF inhibitors (TNFi's) than fusion proteins
- ~50% have disseminated or atypical presentations
- FDA Black box warning for all TNFi's
- TB screening and prophylaxis recommended for all patients on TNFi's
- If latent infection is diagnosed, appropriate prophylaxis guidelines should be instituted, usually INH for 9 months.
- Note that a PPD of >5mm is considered positive for screening rather than the traditional 10 mm.

Issues with TB screening and Latent TB Prophylaxis in RA

- Active RA patients anergic (up to 30%)
  - Negative TB skin test may not exclude latent TB infection
  - Ethnic diversity, frequent BCG vaccination history
  - two step TB skin test if suspicion high
- Fear of combining INH with MTX
- When to add anti-TNF Tx to MTX + INH

INH isoniazid
MTX methotrexate

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Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Guidance for the management of patients with latent tuberculosis infection requiring biologic therapy in rheumatology and dermatology clinical practice

Fabrizio Cantini [a,*], Carlotta Nannini [a], Laura Niccoli [a], Florenzo Iannone [b], Giovanni Delogu [c], Giacomo Garlaschi [d], Alessandro Sanduzzi [e], Andrea Matucci [f], Francesca Prignano [g], Michele Conversano [h], Delia Goletti [i],
on behalf of SAFEBIO (Italian multidisciplinary task force for screening of tuberculosis before and during biologic therapy)

TB Screening Algorithm

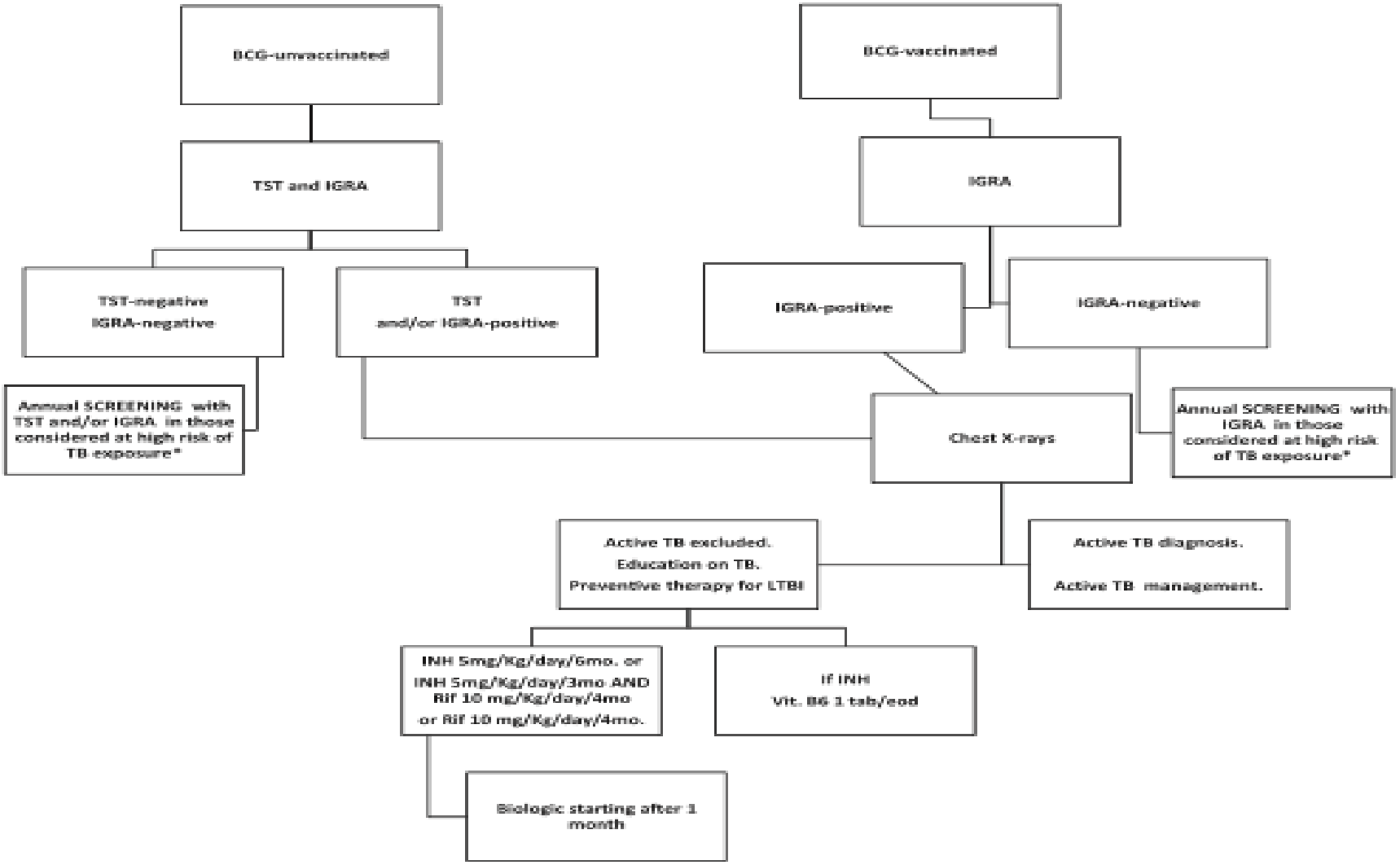

Fig. 1. SAFEBIO recommendations for LTBI detection and active TB prevention in RA patients before biologic therapy starting.

Mini Case 3

- 62 yo male, just started Golimumab 10 weeks ago for his RA. He heard about the Zoster 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

Vaccinations of RA patients

When possible, vaccination should be done prior to Tx

Medications	Pneumovax (anti-pneumococcus)	Fluviral (anti-influenza)	Twinrix Engerix Havrix (anti-hepatitis)	**Avoid live vaccinations (zoster,rabies, oral polio)**
HCQ Hydroxychloroquine		X		
LEF Leflunomide	X	X	X	
MTX Methotrexate	X	X	X	
SSZ Sulfasalazine	X	X		
All Biologic Response Modifiers Agents	X	X	X	X

X: Recommendations

SAAG K. G., American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis Arthritis & Rheumatism Vol. 59 (6), June08, pp 762–784

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?
- Vaccinate even with live vaccines at time of scheduled biologic injection?
- “High dose” Flu vaccine vs. regular Fluvax for RA patients? (recent Mcgill study)

Mini Case 4

- 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

Lymphoma Incidence in RA

Study	Country	# RA Patients	Years of follow-up	SIR for Cancer	SIR for Lymphomas
Gridley (1993)[1]	Sweden	11,683	20	1.0	2.4
Mellenkjaer (1996)[2]	Denmark	20,699	14	1.1	2.4
Isomaki (1978)[3]	Finland	46,101	7	1.1	2.7
Baecklund (1998)[4]	Sweden	11,683	18	–	1.0 (Low act.) 5.4 (Med act.) 25.8 (High act.)

1. Gridley G, et al. J Natl Cancer Inst 1993;85:307-11.
2. Mellemkjaer L, et al. Eur J Cancer 1996;32A:1753-7.
3. Isomaki, et al. J Chron Dis 1978;31:691-6.
4. Baecklund E, et.al. BMJ 1998;317:180-1

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

Mini Case 5

- 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

Monika Østensen

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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, adequately powered, well-designed 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 **Accessed April 3, 2010**

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 CZP)

  Current data suggest that if there is a signal of teratogenicity with anti-TNF agents, it appears small

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

Mini Case 6

- 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)

Anti-TNF treatment and risk of surgical site infections after elective orthopedic surgery in RA

768 RA patients: 1,219 elective orthopedic procedures:

	anti-TNF naïve patients	anti-TNF treatment interrupted, n	anti-TNF treatment continued, n
Procedures, n	1023	104	92
SSI rates	4.0%	5.8%	8.7%*

- Continuing anti-TNF > interrupted anti-TNF before surgery but not statistically different
- Variables significantly associated with increased risk of SSI in all patients:
  - History of SSI or skin infection
  - Elbow, foot or ankle surgery
  - Steroid Use
  - Diabetes
- Continued perioperative use of anti-TNF was not a strong risk factor for SSI

SSI = serious surgical infection

* p=NS for difference between anti-TNF interrupted and anti-TNF continued

den Broeder et al., *J Rheum* 2007;34:689–895.

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

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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

TNF Antagonists: Relative Contraindications

- Current active serious infections
- Chronic/recurrent infections
- History of untreated TB and/or positive PPD test
- Systemic lupus erythematosus?
- Multiple sclerosis, optic neuritis
- Congestive heart failure, ?ILD

Conclusions: Safety

- 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

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

Thank You !