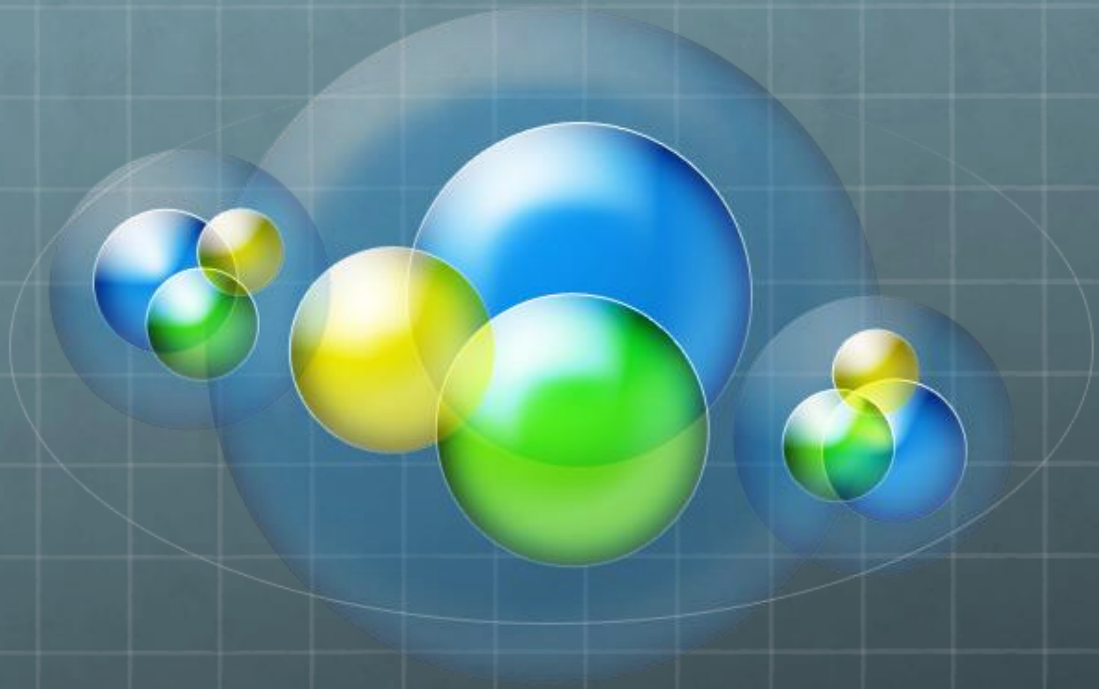


Biologics

A Primer for Primary Care and Other specialists

Julie Jones, DO, RhMSUS

October 2019

Disclosures

- No financial or other conflicts to disclose

Learning objectives

Upon completion of this session, participants will be able to:

- Discuss available biologics for the treatment of RA
- Address patient concerns regarding malignancies when taking biologics
- Decide when to hold biologics In the setting of infections and pre/post-op
- Recommend the correct vaccinations for patients on biologics

Patient Case: Lillian -

RHEUMATOLOGIST EVALUATION

- 10 weeks after the initial evaluation to her PCP
- Physical examination:
  - No nodules or joint deformities
  - 8 swollen joints (MCP 2,3,4 bilaterally and both wrists) and 11 tender joints (MCP 2,3,4 bilaterally, both wrists, both elbows, and right shoulder). Skin over knuckles are red.
- Lillian rated her global assessment of disease activity on a visual analog scale (VAS) as 85/100. She reported severe fatigue.
- Labs:
  - Elevated ESR of 59, CRP at 10 mg/L, RF at 340 u/mL, and ACPA at 35 u/mL
  - Hepatic and renal function were normal, as well as her differential
  - Hgb; 11 g/dL and MCV; 79 fL/red cell were slightly lower than normal
- Imaging:
  - Normal chest X-ray
  - Xrays of the hands and feet: no erosions

Patient Case: Lillian Rheum Follow-up

- Lillian presents 3 months after diagnosis & initiating treatment with MTX 15MG PO QW
- Improvement has been minimal. c/o pain, prolonged stiffness. Depressed. Fatigued.
- Because of pain and fatigue, she is considering early retirement

How to Score the CDAI

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
Add the above values to calculate the CDAI score	**(0-76)**	

CDAI Score Interpretation	
0.0 – 2.8	Remission
2.9 – 10.0	Low Activity
10.1 – 22.0	Moderate Activity
22.1 – 76.0	High Activity

Our patient Lillian:
TJC: 10
SJC: 6
PGA: 6
EGA: 6

CDAI: 28 HIGH ACTIVITY

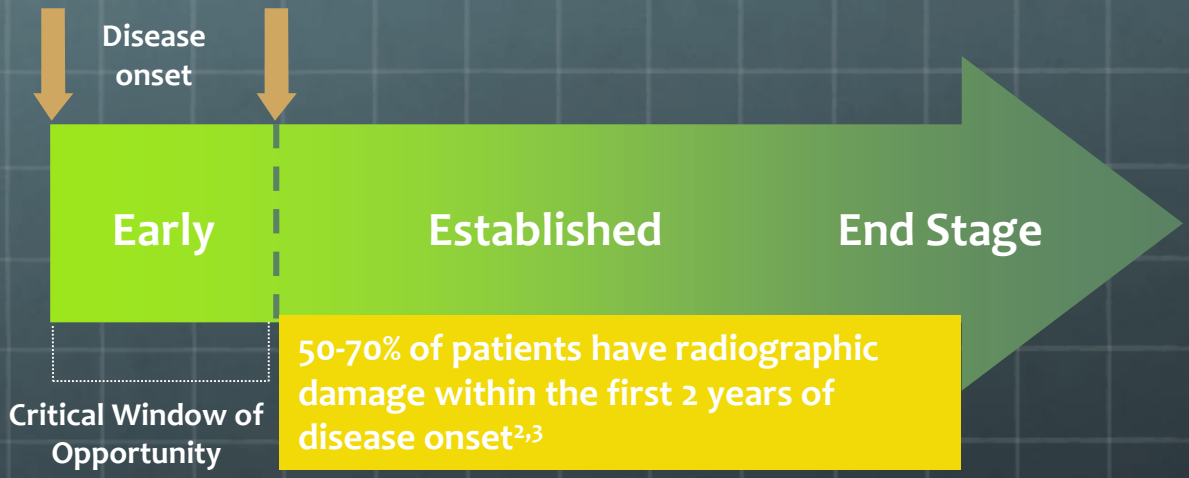
Patient Case: Lillian continued

- Lillian's initial CDAI 33.5
- After 3+ months of MTX, CDAI 28
- Because she experienced symptoms several months prior to diagnosis, she is at higher risk for long term joint damage than she would have had she been diagnosed earlier
- Her Rheumatologist recommends ADDING another drug to her regimen that would hopefully yield greater efficacy

ACR Guidelines Suggest Control of Disease Progression Should Start Early to Limit Joint Damage

"Successful treatment to limit joint damage and functional loss requires early diagnosis and timely initiation of disease modifying agent. The goal of treatment is to arrest the disease and achieve remission."[1]

American College of Rheumatology (ACR) Ad Hoc Committee on Clinical Guidelines



1.Guidelines for the Management of Rheumatoid Arthritis 2002 Update. *Arthritis Rheum*. 2002;46:341.
2. van der Heijde DMFM. *Br J Rheumatol*. 1995:34(suppl 2):74-78.
3. Sundy SS, St. Clair EW. *J Musculoskel Med*. 2002;19:395-403.

Patient case: Lillian continued

- Having determined MTX monotherapy insufficient to achieve treatment goals, Adalimumab is added to MTX
- Patients with IR (incomplete response) to csDMARDs (such as MTX) have been noted to benefit from intensive treatment with addition of a biologic
- After 3 months of Adalimumab + MTX CDAI is now 6.

How to Score the CDAI

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
Add the above values to calculate the CDAI score	**(0-76)**	

CDAI Score Interpretation	
0.0 – 2.8	Remission
2.9 – 10.0	Low Activity
10.1 – 22.0	Moderate Activity
22.1 – 76.0	High Activity

Our patient Lillian:
TJC: 2
SJC: 0
PGA: 2
EGA: 2
CDAI: 6 LOW ACTIVITY

Going back 3 months

- Rheumatologist: As we previously discussed, given your inadequate response to DMARDs, I think it is time to add a biologic to your treatment.
- Patient Lillian: What are my options and which one do you think is best for me?

Question 1

According to the ACR Treatment Algorithm, what is the next step after failing DMARD monotherapy?

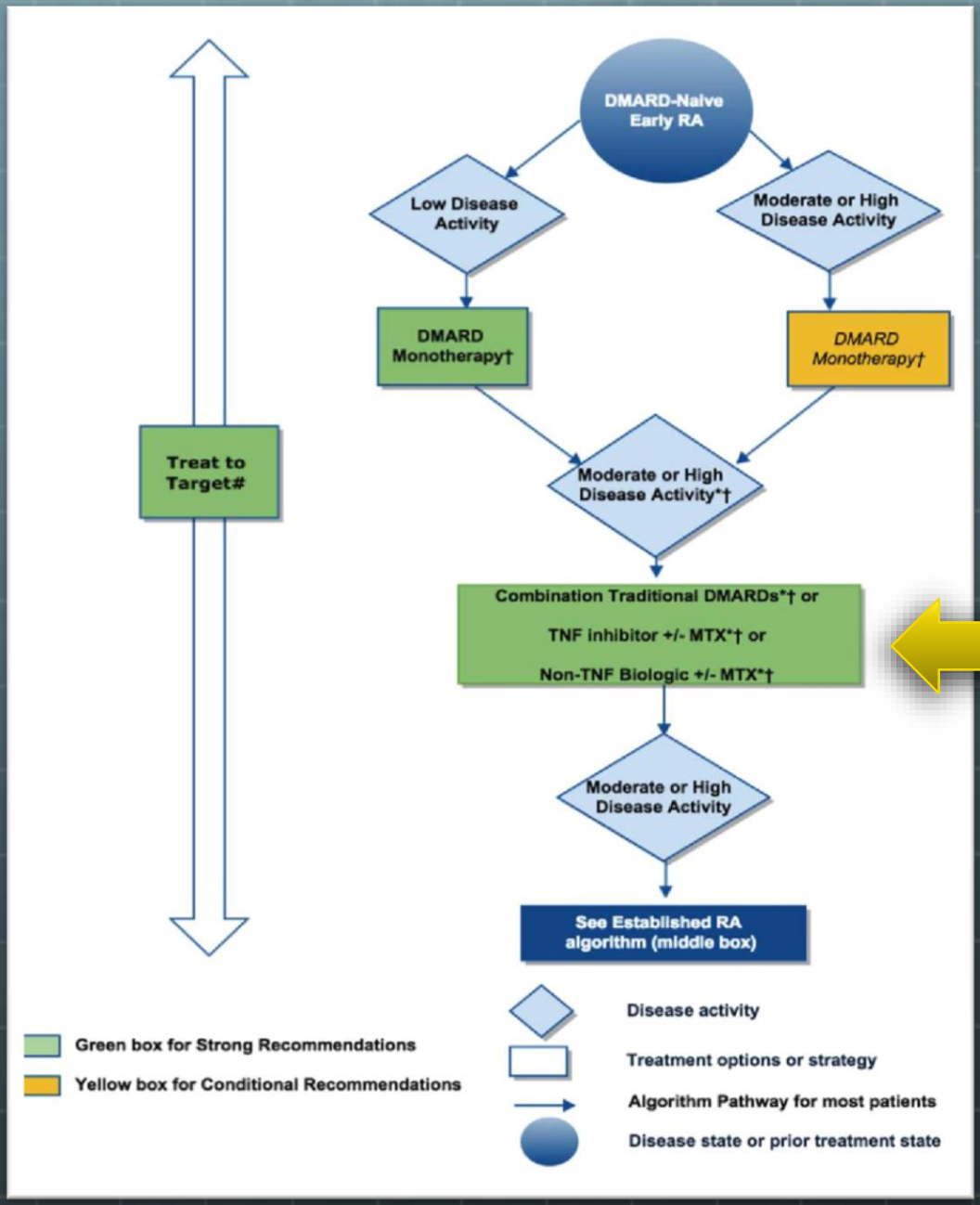
A: Combined DMARD therapy/add an additional DMARD to current therapy

B: Anti-TNF Biologic +/-DMARD

C: non-Anti-TNF Biologic +/-DMARD

D: All of the Above

ACR Treatment Algorithm



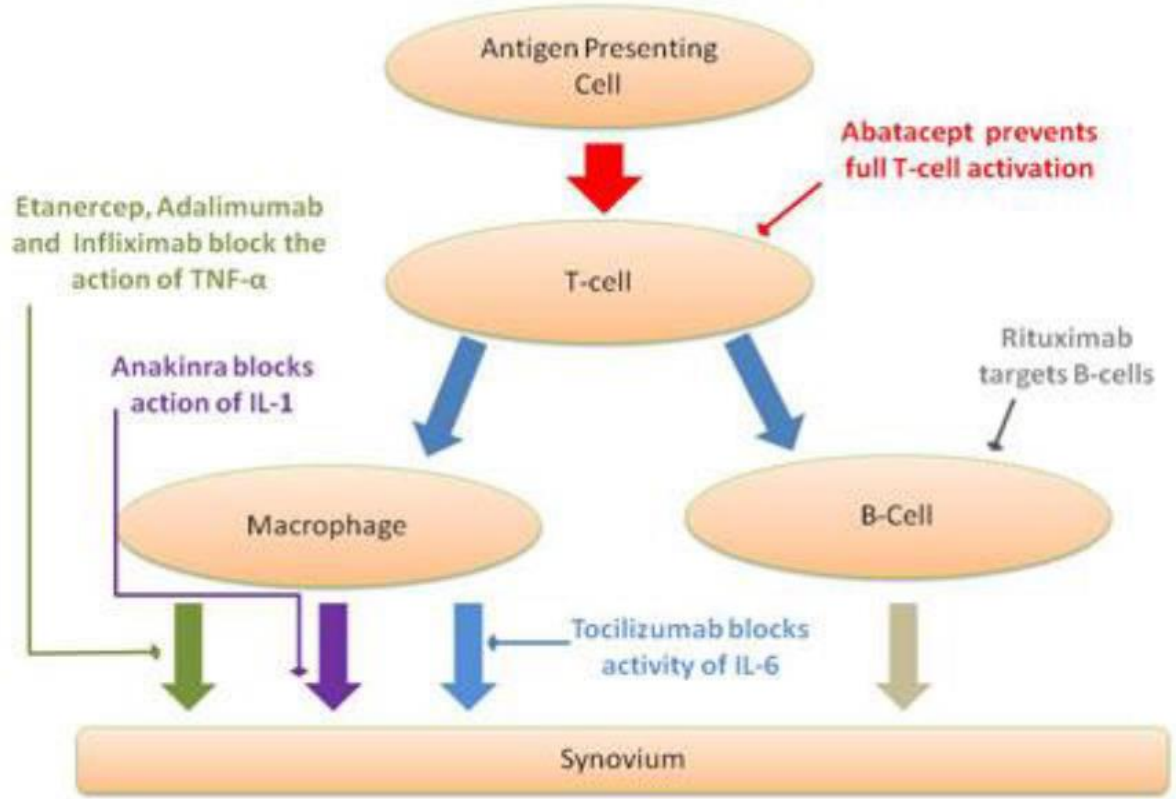
TNF +/- MTX

OR

NON-TNF +/-MTX

Current Biologic Targets

- **Cytokines**: (TNF alpha, IL-1, IL-6)
- T Cell: Co-stimulation (CD 80/86 co-stimulator)
- B cell: (anti-CD 20)



Landmark Developments in the Treatment of RA

- Corticosteroids – 1940s
- Methotrexate – 1980s
- Anti-TNF therapy – 1998

Current Treatments for RA

Nomenclature
c/cs DMARD
t/ts DMARD
b DMARD

- Conventional synthetic (cs) DMARDs
  - Methotrexate
  - Sulfasalazine
  - Hydroxychloroquine
  - Leflunomide
- Targeted synthetic (ts) DMARDs
  - JAK kinase inhib
- Biologic (b) DMARDs
  - Cytokine inhibitors
    - Anti-TNF
    - Anti-IL-6R
    - (Anti-IL-1)
  - Cellular depletion/inhib
    - B cell depleting
    - T cell costimulatory inhib

Biologic DMARDs: Cytokine Inhibitors

- **Anti-TNF**
  - Etanercept, infliximab, adalimumab, certolizumab, golimumab plus Biosimilars
  - All antibodies except etanercept (soluble TNF receptor)
  - Effective as monotherapy or with MTX and other csDMARDs
  - Efficacy: similar despite mechanism (Ab vs receptor)
  - Safety: more infectious risk with high dose infliximab
  - Immunogenicity: highest with infliximab → **use w/MTX**
- **Do not combine two biologic DMARDs**

FDA Approved Biosimilars for Rheumatic Diseases

Biosimilar	Reference Product
Adalimumab-atto (Amjevita)	Adalimumab (Humira)
Adalimumab-adbm (Cyltezo)	Adalimumab (Humira)
Etanercept-szzs (Erelzi)	Etanercept (Enbrel)
Infliximab-abda (Renflexis)	Infliximab (Remicade)
Infliximab-dyyb (Inflectra)	Infliximab (Remicade)
Infliximab-qbtx (Ixifi)	Infliximab (Remicade)

Bridges SL et al, A&R 2018

Biologic DMARDs: Cytokine Inhibitors

- **Anti-IL-6 Agents: Tocilizumab**
  - Effective as monotherapy
  - Effective in MTX inadequate responders
  - Effective in TNF inadequate responders
  - Safety: elevates lipids (via ↓ inflamm); GI perforations

Biologic DMARDs: Cell Based Inhibitors

- B cell depleting agent: Rituximab
  - Immunogenicity: high, use with MTX (+steroids)
  - Efficacy: better in combo w/ MTX than monotherapy
  - Safety: rare risk of Progressive Multifocal Leukoencephalopathy (PML); ?hypogamma?

Tofacitinib:
FDA approved JAK kinase inhibitor

- Tofacitinib inhibits JAK kinase 1/3 > 2
- Oral; Quick onset of action
- Effective as monotherapy or in combination with other non-biologic DMARDs
- Potential side effects: anemia (JAK-2), lipid elevations, neutropenia, LFT elevations

Rheumatologist recommends adalimumab incombination with MTX

- Based on training and clinical experience
- Findings of PREMIER Study

Overall Conclusions

- In MTX-naïve patients with early RA, combination therapy of adalimumab with MTX was superior to either MTX or adalimumab alone in achieving and sustaining
  - Significant clinical outcomes
  - Inhibition of structural damage
- 1 out of 2 patients achieved remission with adalimumab + MTX
- Adalimumab + MTX was generally safe and well tolerated

… But my neighbor took this drug and got cancer in her blood

- RA increases risk of Lymphoma 3 to 10 fold, chronic inflammation
- Original studies on TNFi's and increased lymphoma on patients with advanced long standing, poorly controlled RA and increased inflammation
- New studies and information from 2015 -2017 show no increased risk in patients on TNFi's

Recommendations regarding malignancies

- History of solid organ tumors
  - Recommendations same as those with no history
- Previous history of lymphoproliferative malignancy
  - Use rituximab over TNFi
- Previous history of melanoma/non-melanoma
  - Use DMARDs over Biologics
- Green=strong Yellow=conditional or low level

CHF and TNFi's

- Use combination DMARDs or non-TNF biologics over TNFi's in CHF
- TNF's can be used in fully compensated CHF

Patient case: Lillian continued

- Having determined MTX monotherapy insufficient to achieve treatment goals, Adalimumab is added to MTX
- Patients with IR (incomplete response) to csDMARDs (such as MTX) have been noted to benefit from intensive treatment with addition of a biologic
- After 3 months of Adalimumab + MTX CDAI is now 6.

How to Score the CDAI

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
Add the above values to calculate the CDAI score	**(0-76)**	

CDAI Score Interpretation	
0.0 – 2.8	Remission
2.9 – 10.0	Low Activity
10.1 – 22.0	Moderate Activity
22.1 – 76.0	High Activity

Our patient Lillian:
TJC: 2
SJC: 0
PGA: 2
EGA: 2
CDAI: 6 LOW ACTIVITY

Should I get my flu shot?

Vaccines

- What vaccines are recommended for patient while on biologics? (Always preferred to give prior to initiating)
  - See specific recommendations for timing of vaccines and infusion/injections of biologics
- Flu Vaccine: High dose if over 65;
  - CDC does not recommend High dose and not FDA approved for immunosuppressed patients under age 65
  - Non Flu-mist or live vaccine
- Pneumonia per CDC recs
- Hepatitis B and HPV
- Shingles
  - 2 dose Shingrix, no live vaccine

6 months later

Patient presents to your office with severe cough, fever, night sweats, increased fatigue, worsening over past 4 weeks. She was seen in **Urgent care and treated with antibiotics for CAP with no improvement.**

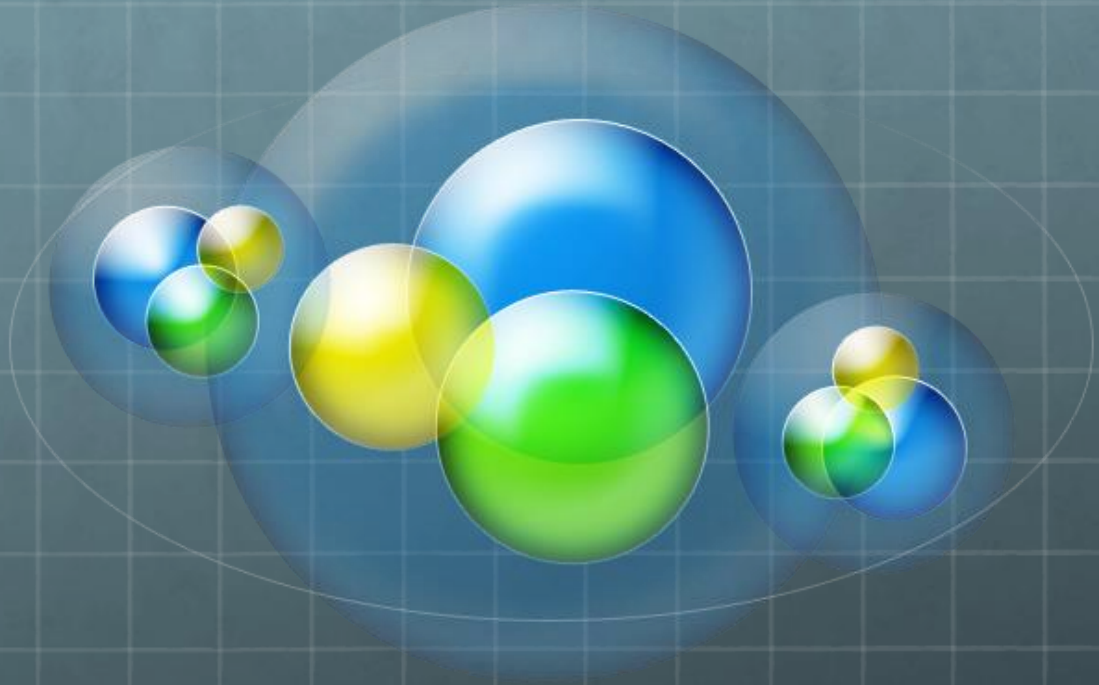
Patient has had 10 pound weight loss and appears generally unwell.

Admitted to hospital for further evaluation.

Found to have **disseminated histoplasmosis.** Acquired while working cleaning out family barn. Exposed to Bat droppings.

Infections

- Consider opportunistic infections, especially fungal in patients on biologics
- TNFis associated with reactivation of latent TB and hepatitis B
  - Screen prior to initiating therapy
  - Rescreen if new exposure or travel to indigent area



Know when to hold ‘em

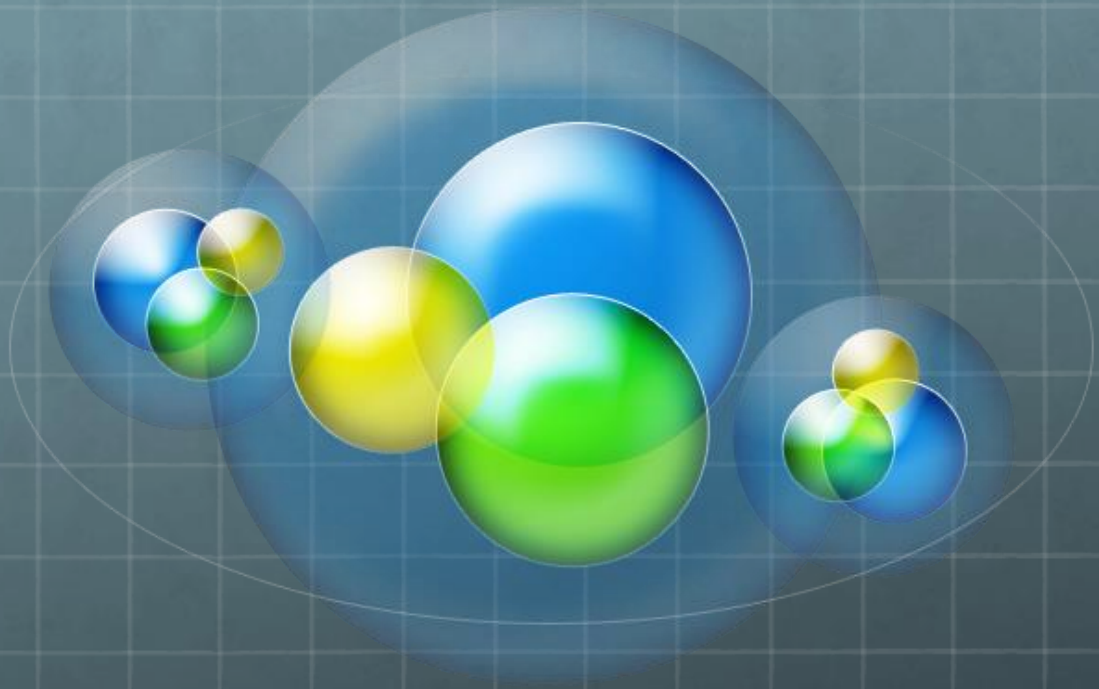
Infections and pre/post op management

Do I have to stop my biologic if I get a cold or other infection?

- Most serious risk of infection in patients with RA is uncontrolled inflammation/poorly controlled disease
- Immunosuppressive medication with highest risk of infection for patients with RA is prednisone (greater than 10 mg daily)
- Not always necessary to hold if on antibiotics
- Hold for infection if
  - Hospitalized
  - Fever greater than 102 or greater than 101 if on above prednisone or other serious immunosuppressive states (chemo, organ transplants)
  - Consider steroid use, age and co-morbidities

Pre/post Op Management of Biologics

- Text to be added



Know when to fold ‘em

When is treatment considered a failure

Remission

ACR/EULAR recommended definition, A&R 2011*

- Scores must all be ≤ 1:
  - Tender joint count
  - Swollen joint count
  - CRP (**mg/dL**)
  - Patient global assessment
- Or SDAI ≤ 3.3

Treatment Failure

- General recommendation is 3 month trial before considering treatment failure
- Maximize dose
  - Can increase dose and/or interval with some biologics
- Discontinue sooner if patient intolerance or significant side effects including lab abnormalities

ACR Algorithm for Treatment of Established RA

Single TNFi failure, switch to second TNFi.

Second TNFi failure, switch class