RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

4th Annual National Conference

September 21–23, 2023

Biologics Update for Rheumatoid Arthritis

Betsy Kirchner NP

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Objectives

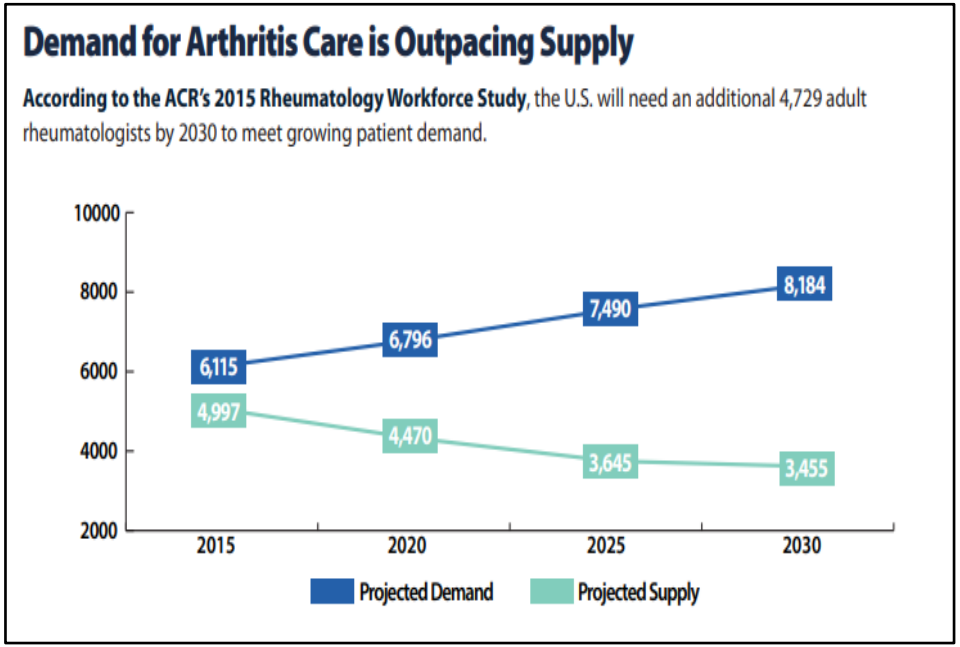
Identify medications to avoid given a patient's past medical history and comorbidities

Consider a patient's current medical status and future plans when initiating therapy

Discuss reasons biologics are discontinued and strategies to avoid discontinuation

Why are we here?

- APPs in US Healthcare/Rheum
  - Projected ratio of physicians (primary care and specialty care) to APRNs will fall from 3.6-to-1 (2015) to 1.9-to-1 (2030)[1]
  - Shortage of rheumatologists
  - Patients with RA seen in practices employing NPs or PAs had lower RA disease activity over 2 years compared to those seen in rheumatologist-only practices[2]
  - APPs write 1/3 of all prescriptions in US[3]



1. AANP Sept 4, 2019 https://www.aanp.org/news-feed/nurse-practitioner-rheumatology-workforce-could-this-be-you

2. Solomon DH, Fraenkel L, Lu B, et al. Comparison of Care Provided in Practices With Nurse Practitioners and Physician Assistants Versus Subspecialist Physicians Only: A Cohort Study of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2015 Dec;67(12):1664-70. doi: 10.1002/acr.22643. PMID: 26096922

3. Coey SK. Digital venture shines light on the pharma prescribing power of nurse practitioners and physician assistants. https://www.fiercepharma.com/marketing/new-venture-brings-to-light-prescribing-power-nps-and-pas

Available Biologics and Targeted Synthetics for Rheumatic Immune-Mediated Inflammatory Diseases

Anti-CD20 Antibody
- Rituximab

BLyS inhibitor
- Belimumab

Interferon receptor antagonist
- Anifrolumab

IL-1 antagonists
- Anakinra
- Canakinumab
- Rilonacept

IL-6 antagonists
- Sarilumab
- Tocilizumab

IL-12/23 antagonist
- Ustekinumab

IL-17 antagonists
- Ixekizumab
- Secukinumab

IL-23 antagonists
- Guselkumab
- Rizankizumab

JAK inhibitors
- Baricitinib
- Tofacitinib
- Upadacitinib

T cell co-stimulation inhibitor
- Abatacept

TNFα inhibitors
- Adalimumab
- Certolizumab
- Etanercept
- Golimumab
- Infliximab

Biologic Initiation Checklist

- ☐ **Labs**
- ☐ Patient preferences
- ☐ Previous biologic trials
- ☐ Insurance/cost
- ☐ Past medical history and comorbidities
- ☐ Infection history
- ☐ Vaccination history
- ☐ Pregnancy status
- ☐ Future surgical plans

Baseline Labs

- CBC with differential
- CMP
- Tuberculosis
- Hepatitis B/C
- HIV in high risk patients
- Lipid panel for IL-6 and JAKi

Rheumatology (Oxford). 2019;58(2):e3-

Follow-up Lab Monitoring

None required per package insert*	Lab monitoring required per package insert
• Abatacept • Anifrolumab • Belimumab • IL-12/23 antagonist • IL-17 antagonist • IL-23 antagonist • TNF inhibitor	• Rituximab • IL-1 antagonist • IL-6 antagonist • JAK inhibitor

**unless receiving concomitant conventional DMARD*

[package inserts]

Comorbid Conditions

Heart failure	Demyelinating disease	Malignancy
Pulmonary disease	Diverticular disease	History of cardiac event or thrombosis

Heart Failure

TNF inhibitors

- **Canadian labeling**: all contraindicated in moderate-to-severe CHF (NYHA class III-IV)
- **US labeling**:
  - Infliximab: doses >5 mg/kg contraindicated in patients with NYHA class III-IV CHF
  - All others: “use with caution in patients with HF or decreased left ventricular function; worsening and new-onset HF reported”
- **2021 ACR RA guidelines:** non-TNF recommended in NYHA class III-IV CHF

Adalimumab [package insert]
Arthritis Rheumatol. 2021;73(7):1108-1123.

CHF = congestive heart failure
NYHA = New York Heart Association

Demyelinating Disease

TNF inhibitors

- Rare cases of **new onset or exacerbation** of clinical symptoms and/or radiographic evidence of **CNS demyelinating disease**
  - multiple sclerosis (MS)
  - optic neuritis
  - peripheral demyelinating disease (Guilain-Barré syndrome)
- *Use with caution in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders*

Adalimumab [package insert]

Demyelinating Disease

IL-6 antagonists

- **Tocilizumab**
  - Impact of treatment on demyelinating disorders is not known
  - Rare cases of MS and chronic inflammatory demyelinating polyneuropathy reported in clinical studies
  - *Use with caution in patients with preexisting or recent onset CNS demyelinating disorders*
- **Sarilumab**
  - No warnings in manufacturer prescribing information

Tocilizumab [package insert]
Sarilumab [package insert]

Pulmonary Disease: ILD

TNF inhibitors

- Reports of ILD in 0.5-0.7% of patients with RA in Japanese post-marketing safety studies of infliximab, etanercept, and adalimumab

- British Society for Rheumatology biologic safety guidelines caution use in patients with poor respiratory reserve

Rheumatology (Oxford). 2019;58(2):e3-e42.

ILD = interstitial lung disease

Pulmonary Disease: COPD

Abatacept

- **ASSURE trial**: in patients with COPD taking abatacept (n=52), increased risk of pulmonary adverse events compared to placebo (43% vs 24%)
- **Real-world observational study**: no increased risk of pulmonary adverse events in patients with COPD taking abatacept (n=1807) compared to matched cohort of patients receiving other biologics (HR 0.87; 95% CI 0.68-1.12)

Arthritis Rheum. 2006;54(9):2807-2816
Semin Arthritis Rheum. 2019;49(3):366-372

COPD = chronic obstructive pulmonary disease

Diverticular Disease

IL-6 antagonists, JAK inhibitors

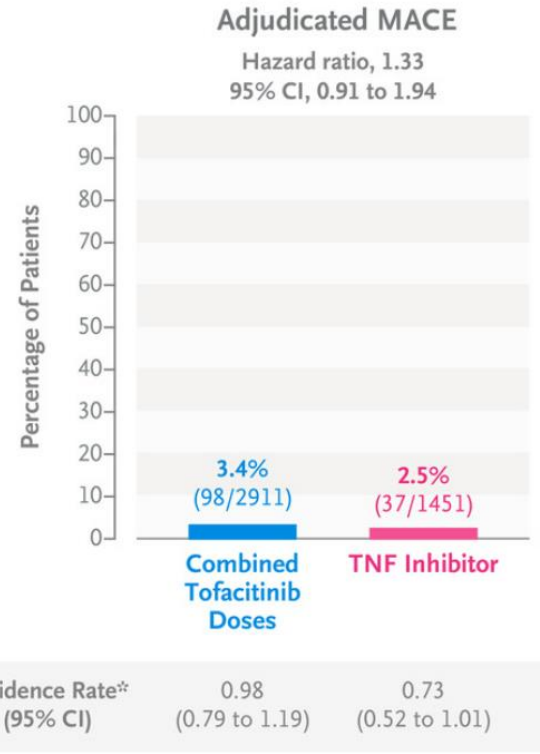
- Gastrointestinal perforations reported in trials, primarily as complications of diverticulitis
- Risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids
- Use with caution in patients at increased risk for GI perforation

Tocilizumab [package insert]
Tofacitinib [package insert]

History of Cardiac Events

JAK inhibitor boxed warning

- In RA patients ≥50 years of age with ≥1 cardiovascular risk factor:
- ↑ risk of MACE
- ↑ risk of thrombosis



N Engl J Med 2022; 386:316-326.

MACE = major adverse cardiovascular event

ORAL Surveillance Study

Cardiovascular risk factors

- Current cigarette smoker
- Hypertension
- HDL <40 mg/dL
- Diabetes mellitus
- Family history of premature coronary heart disease
- Extra-articular RA
- History of coronary artery disease

Significant MACE risk factors

- Current smoking (HR=2.18)
- Aspirin use (HR=2.11)
- Age ≥65 years (HR=1.81)
- Male sex (HR=1.81)

N Engl J Med 2022; 386:316-326.

Summary: Comorbid Conditions

Heart failure
- Avoid TNFi

Demyelinating disease
- Avoid TNFi, tocilizumab

Malignancy
- Consider rituximab
- Caution with TNFi in malignant melanoma
- Caution with JAKi in lung cancer

Pulmonary disease
- Avoid TNFi in ILD
- Avoid abatacept in COPD

Diverticular disease
- Avoid IL-6i, JAKi

History of cardiac event or thrombosis
- Avoid JAKi

Infection Risk

US Boxed Warning for serious infections

IL-6, JAKi, TNFi	Rituximab
• Tuberculosis • Invasive fungal infections • Bacterial, viral, and other opportunistic infections	• Hepatitis B reactivation • Progressive multifocal leukoencephalopathy

- Risks vs benefit of treatment should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection
- Serious infections more common in patients taking concomitant immunosuppressants such as methotrexate or corticosteroids

[package inserts]

Vaccination History

Vaccine	Indication	Level of Recommendation
High-dose or adjuvanted flu vaccine	· Age >65 · Age >18 and <65 on immunosuppressive medication	Conditional for high-dose over regular dose
Pneumococcal vaccination	· Age <65 on immunosuppressive medication	Strong
Recombinant zoster	· Age >18 on immunosuppressive medication	Strong
HPV	· Age >26 and <45 on immunosuppressive medication and not previously vaccinated	Conditional

Arthritis Care Res (Hoboken). 2023;75(3):449-464.

Special Vaccine Considerations – Herpes Zoster

↑ **risk herpes zoster infection with JAKi:**

- Tofacitinib: 1% to 5%
- Upadacinitib: ≤4%
- Baricitinib: 1%

Warnings of reactivation in **IL-6 antagonist** prescribing information

[package inserts]

Special Vaccine Considerations – RTX Timing

Medication management at the time of non-live attenuated vaccine administration

	Influenza vaccination	Other non-live attenuated vaccinations
Methotrexate	Hold methotrexate for 2 weeks *after* vaccination*	Continue methotrexate
Rituximab	Continue rituximab**	Time vaccination for when the next rituximab dose is due, and then hold rituximab for at least 2 weeks after vaccination
Immunosuppressive medications other than methotrexate and rituximab	Continue immunosuppressive medication	Continue immunosuppressive medication

*Hold only if disease activity allows. Non-rheumatology providers, e.g., general pediatricians and internists, are encouraged to give the influenza vaccination and then consult with the patient's rheumatology provider about holding methotrexate to avoid a missed vaccination opportunity.

**Give influenza vaccination on schedule. Delay any subsequent rituximab dosing for at least 2 weeks after influenza vaccination if disease activity allows.

= Conditional recommendation

Arthritis Care Res (Hoboken). 2023;75(3):449-464.

Pregnancy Plans

Table 2. Recommendations regarding medication use for men with rheumatic and musculoskeletal disease who are planning to father a child

Strongly recommend continuing	Conditionally recommend continuing	Strongly recommend discontinuing	Conditionally recommend discontinuing	Unable to make a recommendation due to limited data
Azathioprine/ 6-mercaptopurine Colchicine Hydroxychloroquine Tumor necrosis factor inhibitors (all)	Anakinra Cyclooxygenase 2 inhibitors Cyclosporine Leflunomide Methotrexate Mycophenolate mofetil Mycophenolic acid Nonsteroidal anti-inflammatory drugs Rituximab Sulfasalazine *(semen analysis if delayed conception)* Tacrolimus	Cyclophosphamide *(discontinue 12 weeks prior to attempted conception)*	Thalidomide *(discontinue 4 weeks prior to attempted conception)*	Abatacept Apremilast Baricitinib Belimumab Secukinumab Tocilizumab Tofacitinib Ustekinumab

Arthritis Care Res (Hoboken). 2020;72(4):461-488.

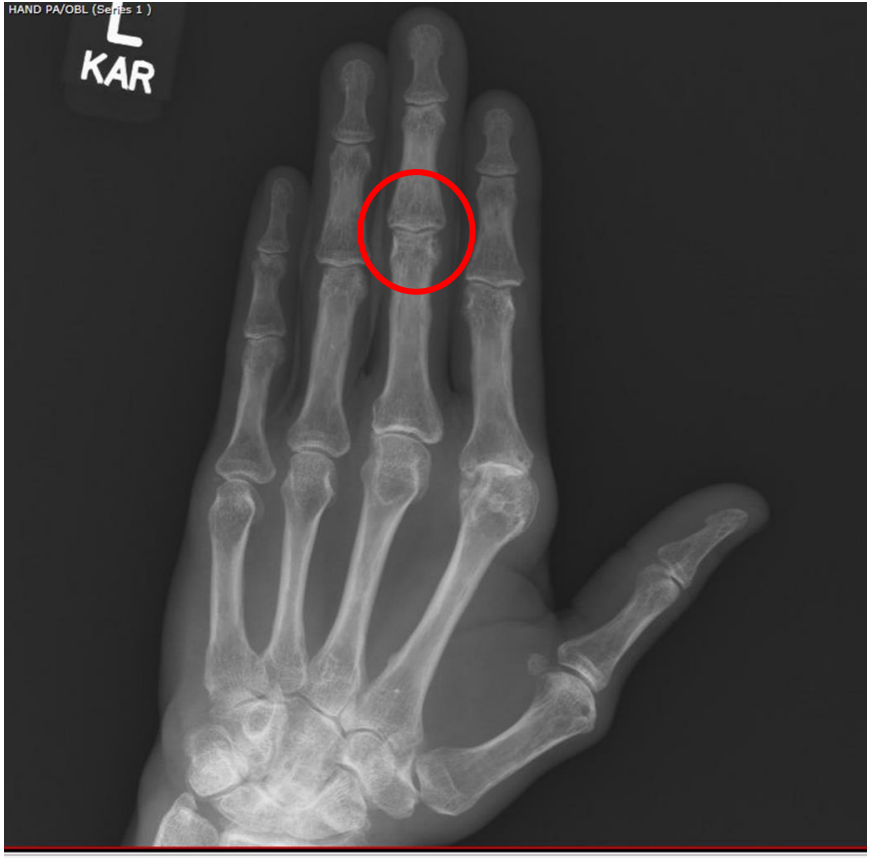
MEDICATIONS TO WITHHOLD PRIOR TO SURGERY***		
BIOLOGICS: WITHHOLD these medications through surgery		**Recommended timing of surgery since last medication dose**
Infliximab (Remicade)	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Adalimumab (Humira)	Every 2 weeks	Week 3
Etanercept (Enbrel)	Every week	Week 2
Golimumab (Simponi)	Every 4 weeks (SQ) or every 8 weeks (IV)	Week 5 Week 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
IL-17-Secukinumab (Cosentyx)	Every 4 weeks	Week 5
Ustekinumab (Stelara)	Every 12 weeks	Week 13
Ixekizumab (Taltz)†	***Every 4 weeks***	***Week 5***
IL-23 Guselkumab (Tremfya)†	***Every 8 weeks***	***Week 9***
JAK inhibitors WITHHOLD this medication 3 days prior to surgery*		
Tofacitinib (Xeljanz):	***Daily or twice daily***	***Day 4***
Baricitinib (Olumiant)†	***Daily***	***Day 4***
Upadacitinib (Rinvoq)†	***Daily***	***Day 4***
NOT-SEVERE SLE: WITHHOLD these medications 1 week prior to surgery	**Dosing Interval**	**1 week after last dose**
Mycophenolate mofetil	Twice daily	**1 week after last dose**
Azathioprine	Daily or twice daily	1 week after last dose
Cyclosporine	Twice daily	**1 week after last dose**
Tacrolimus	Twice daily (IV and PO)	**1 week after last dose**
Rituximab (Rituxan)	Every 4-6 months	Month 7
Belimumab IV (Benlysta)	***Monthly***	***Week 5***
Belimumab SQ (Benlysta)	***Weekly***	***Week 2***

Arthritis Care Res (Hoboken). 2022;74(9):1399-1408.

Mr. CCF: June 2019

- 64 year old Black male
- History of severe CTS (bilat) since ~2006
- s/p arthroscopic carpal tunnel releases (right 12/18, left 1/19).
- Worsening stiffness in hands in the morning since a month after the second surgery
- Sudden onset, spread to other joints

- RF negative, CCP negative (2009)
- RF positive, CCP >250 (2019)



Primary Non-adherence

- National rheumatology EHR/pharmacy claims data
- Biologics, csDMARDs, tsDMARDs
- Medicare n=1239
  - 1577 meds
  - Mean age 69
- Commercial n=258
  - 317 meds
  - Mean age 64
- 20 to 44% of newly prescribed DMARDs were not filled within 6 months

Curtis J, Su Y, Clinton C, et al. Primary Non-adherence to Biologics and Immunomodulatory Therapies for Rheumatoid Arthritis, Psoriatic Arthritis, and Spondyloarthritis Using Linked EHR and Pharmacy Claims Data [abstract]. Arthritis Rheumatol. 2022; 74 (suppl 9). https://acrabstracts.org/abstract/primary-non-adherence-to-biologics-and-immunomodulatory-therapies-for-rheumatoid-arthritis-psoriatic-arthritis-and-spondyloarthritis-using-linked-ehr-and-pharmacy-claims-data/ 2199

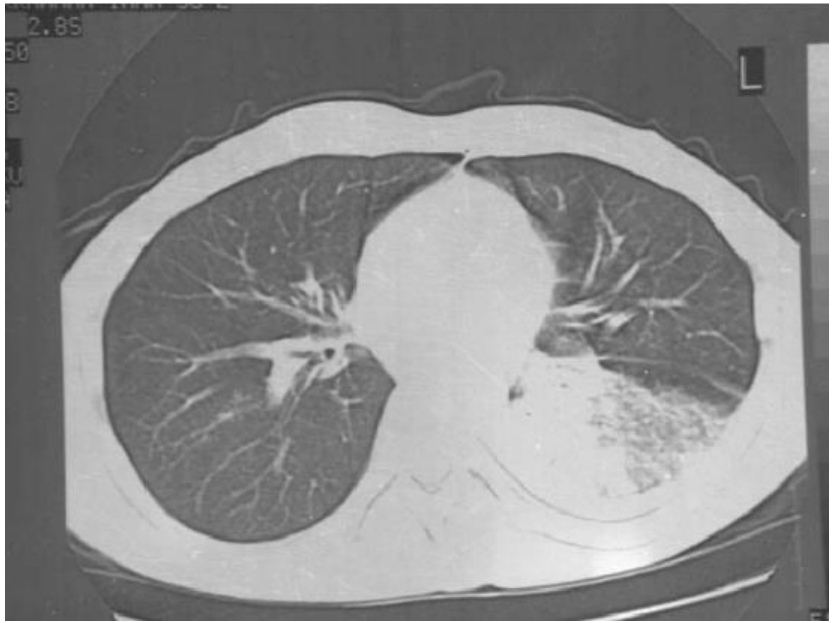
Adherence

- Colombian study [1]
  - Self-reported adherence (CQR)
  - 564 RA patients
  - ~50% scored >80 (=adherent)
  - Factors associated with nonadherence included Rx dispensing delays, infections, and delay between disease onset and rheum consult.
- German study [2]
  - Self-reported (CQR and BMQ)
  - 137 RA patients
  - ~68% scored >80 (=adherent)
  - Adherence dependent on patient's belief in necessity, medication concerns, patient age.

1.Cubillos Escobar E., Maldonado-Canon K., Coral Alvarado P. et al. Associated Factors with Treatment Adherence in Rheumatoid Arthritis: A Cross-Sectional Analytic Study of Colombian Patients. ARD volume 81, supplement 1, year 2022, page 1254. AB0254
2. Jugel C. ,Baerwald C., Seifert O. Medication Adherence and Beliefs About Medication in Patients with Rheumatoid Arthritis. ARD volume 81, supplement 1, year 2022, page 1249. AB0244

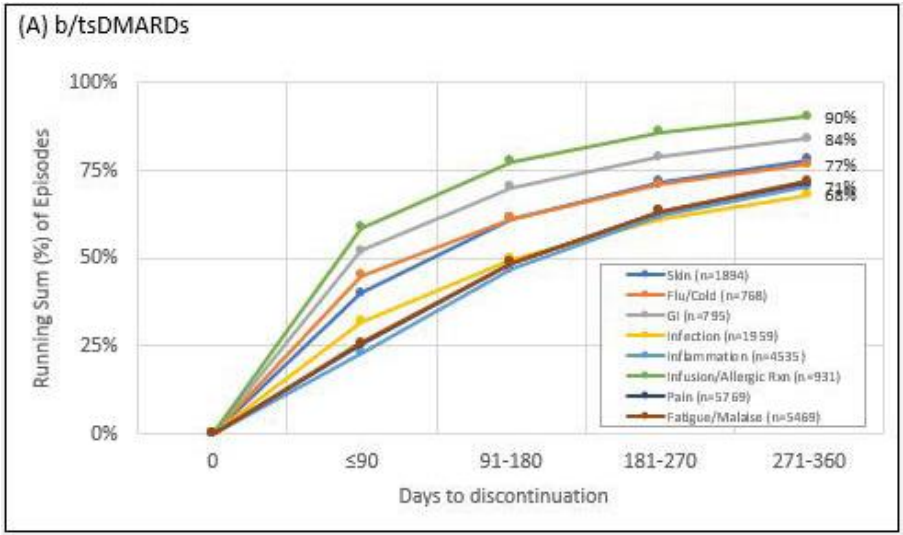
Mr. CCF Starts Treatment

- MTX monotherapy
  - Tolerates
  - Maximizes dosing
  - Inadequate responder
- Starts SC anti-TNF
  - Tolerates
  - Meets ACR/EULAR definition of remission
- Switches to IV anti-TNF
  - Tolerates
  - Still in remission
  - Gets a serious infection
  - MTX and anti-TNF are held



Reasons for switch/discontinuation

- Study of >10K US RA patients who discontinued b/ts 2017-2021[1]
  - 5% lost to follow up, 21% attrition
  - 74% clinical
    - 2% met treatment goals
    - 54% lack of efficacy
    - 37% non-manageable condition
    - 41% manageable condition



1. Huston K, Adams C, Helfgott S, et al. Reasons for Early Discontinuation of Targeted Synthetic (ts) or Biologic (b) DMARDs; Chart Review of 20,343 Drug Episodes Given to Patients with Rheumatoid Arthritis [abstract]. Arthritis Rheumatol. 2022; 74 (suppl 9). https://acrabstracts.org/abstract/reasons-for-early-discontinuation-of-targeted-synthetic-ts-or-biologic-b-dmards-chart-review-of-20343-drug-episodes-given-to-patients-with-rheumatoid-arthritis/. 0264

Cost of Switching Biologics

- 25% within 1st year, +$14,000 [1]
- 17% within 1st year, +$1,135 [2]
- 22.5% within 1st year, +$4,460 [3]
- 16.7% within 1st year, +$2,343 [4]
- 12% within 1st year, 25% increase in cost [5]

1. Wu JJ, Pelletier C., Ung B, Tian M., Khilfeh I., Curtis J. Treatment Switch Patterns and Healthcare Costs in Biologic-Naïve Patients with Psoriatic Arthritis. Adv Ther (2020) 37:2098-2115 doi 10.1007/s12325-020-01262-9
2. Dalen J, Luttropp K, Svedbom A et al.. Healthcare-related costs associated with switching SC TNF-I in the treatment of inflammatory arthritis: a retrospective study. Adv Ther (2020) 37:3746-3760 doi 10.1007/s12325-020-01425-8
3. Yi E, Dai D, Piao O et al. Health care utilization and cost associated with switching biologics within the first year of biologic treatment initiation among patients with AS. J Manag Care Spec Parm 2021:27(1):27-36
4. Gu T, Mutebi A, Stolshek B, et al. Cost of Biologic Treatment Persistence or switching in RA. Am J Manag Care. 2018;24(Spec Issue No. 8):SP338-SP345.
5. Rashid N, Lin A, Aranda G, et a;.(2016) Rates, factors, reasons, and economic impact associated with switching in rheumatoid arthritis patients newly initiated on biologic disease modifying anti-rheumatic drugs in an integrated healthcare system, Journal of Medical Economics, 19:6, 568-575, DOI: 10.3111/13696998.2016.1142448

“Cost” of Switching Biologics

- Cost to office/department
  - New medication teaching
  - Prior authorization
  - Appeal
  - Lab monitoring/follow up
  - MyChart/phone messages
- Cost to patient
  - Time on phone with insurance and/or pharmacy and/or patient assistance program and/or office
  - Labs
  - Stress

Setting reasonable expectations

- Post-hoc analysis of large trial
- 2019 (over 1600 RA patients)
- “Attenuation of inflammation”
  - Zero swollen joints (out of 66)
  - CRP <0.6 mg/dL

Attenuation of Inflammation	
	Week 26
Placebo	41 (6.3%)
Drug #1	60 (18.3%)
Drug #2	187 (28.7%)

Bessette L, Kakehasi A, Basu N, et al. Effect of *2 drugs*, and Placebo on Residual Pain Among Patients with Rheumatoid Arthritis Whose Inflammation Was Attenuated After Three and Six Months of Treatment [abstract]. *Arthritis Rheumatol.* 2022; 74 (suppl 9). # 0297

More reasonable expectations

- CorEvitas RA registry
- On a b/tsDMARD as of 2012
  - 7800 patients
  - Almost 9600 b/ts starts
- Outcome = time to switch to different MOA
- Unadjusted risk for severe vs mild pain (HR=1.98; 1.60–2.44)
- Adjusted risk for severe vs mild pain after accounting for confounders (HR=1.37; 1.02–1.86)
- Twice as likely to switch if you're in pain, *independent of disease activity scores*

	Mild Pain	Severe Pain
Smoker	15%	23%
Obese	40%	52%
Depressed	28%	43%
Fibromyalgia	3%	12%
Opioids	18%	49%

Baker J, Symons J, Janak J, et al. Pain and Treatment Switching Among Patients in the CorEvitasTM Rheumatoid Arthritis Registry [abstract]. Arthritis Rheumatol. 2022; 74 (suppl 9). #1590

Mr. CCF has recovered from his CAP

- Spent one night in the hospital for IV antibiotics
- Discharged home on 10 days of oral antibiotics and prednisone taper
- On 2L O2 per NC while in-house but no O2 requirements upon d/c
- 3 weeks after discharge he is in your office telling you his breathing is fine but his arthritis is starting to flare
- Now what?

Restarting biologics after a serious infection

- 2018 BSRBR report
- Almost 22K patients on their 1st TNFi 2008 -2016
- 1583 has at least one SI
- Followed for one year: any further SI?
- Rate of recurrent SI: 43.6% (off biologic @ Day 60); 23.2% (continued TNFi); 12.1% (switched classes).

Subesinghe S, Rutherford AI, Byng-Maddick R, et al. Biologic prescribing decisions following serious infection: results from the British Society for Rheumatology Biologics Register—Rheumatoid Arthritis, *Rheumatology*, Volume 57, Issue 12, December 2018, Pages 2096–2100, https://doi.org/10.1093/rheumatology/key198

Conclusions

- There are many factors to consider when initiating, maintaining, or restarting patients on biologics.
- Good communication is key in order to be aware of changes in health status, difficulties in obtaining or continuing biologics, etc.
- Setting reasonable expectations (both with patients and for ourselves!) may help prevent switching or discontinuing biologics too soon.