



# Rheumination

Alan R. Erickson, MD, M.Ed  
FACR, FACP  
Rheumatology and Internal Medicine  
Associate Professor  
Assistant Dean of Student Affairs  
Nebraska Medicine  
University of Nebraska College of Medicine.



## Disclosures

- None
  - “I’m just a simple country doc hiding in a university”





## Goals

- To expose the audience to new and relevant medical information in the field of Rheumatology.
- To discuss how this information impacts patients with rheumatic diseases.
- To examine how this information impacts providers and the numerous specialists that participate in the care of these complex patients.



# Rheumatoid Arthritis

## Interstitial Lung Disease

- There are many disease states that can impact the lung of a patient with RA.
  - RA nodules
  - Pneumonitis
  - Infections
  - Cancer
  - Bronchiolitis
  - Obliterans bronchiolitis
  - ILD
- Risk factors for ILD
  - Male sex, tobacco use, RF(+), CCP(+)



# Rheumatoid Arthritis

## Interstitial Lung Disease

- There may also be a genetic risk factor that is seen with IPF (Juge et al., NEJM, 2018).
  - The gain-of-function MUC5B promoter variant rs35705950
- On CT scan the pattern may be more of a UIP pattern and this pattern may actually herald the onset of RA
  - This would be in distinction to MTX induced hypersensitivity pneumonitis which is typically early in therapy and is subacute (Kiely, et al., BMJ, 2019).
  - <https://www.ncbi.nlm.nih.gov/pubmed/30345907>
  - <https://www.ncbi.nlm.nih.gov/pubmed/31061059>



# Rheumatoid Arthritis

## RA Drugs

- Large topic but a few pearls for the newest drugs/biological therapy
- For most of these drugs the patient should be screened for hepatitis B, C, and TB
  - Hep B-s ag
  - Hep B-s ab
  - Hep B-core IgM
  - Hep C ab
  - TB tine or TB quantiferon
- Avoid concomitant use with other biologicals
- Avoid the administration of live vaccines
- Increased risk of certain malignancies to include lymphoma
- The Rheumatologist, 2019. <https://www.the-rheumatologist.org/article/rheumatology-drugs-at-a-glance-part-3-rheumatoid-arthritis/10/>



# Rheumatoid Arthritis

## RA Drugs

- Abatacept
  - Selective T cell co-stimulation modulator
  - COPD patients may develop more respiratory adverse events
- Anti-TNF therapies (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)
  - Infections to include fungal
  - Demyelination
  - Lupus-like syndromes
  - Heart failure
- The Rheumatologist, 2019. <https://www.the-rheumatologist.org/article/rheumatology-drugs-at-a-glance-part-3-rheumatoid-arthritis/10/>



# Rheumatoid Arthritis

## RA Drugs

- Tofacitinib
  - JAK inhibitor that is a oral small molecule
  - Increased risk of GI perforations
  - Decreased white cells, increased lipid and increased liver enzymes
  - Questionable/probable risk of thrombosis
- Baricitinib
  - JAK inhibitor
  - Increased risk of thrombosis
- Tocilizumab
  - IL-6 RA
  - GI perforations
  - Decreased white cells, increased lipid and increased liver enzymes
- The Rheumatologist, 2019. <https://www.the-rheumatologist.org/article/rheumatology-drugs-at-a-glance-part-3-rheumatoid-arthritis/10/>



# Rheumatoid Arthritis

## Myocarditis

- It has been suggested that RA has an increased risk of myocarditis (Amigues et al., Arthritis Rheumatol., 2019)
- With the use of PET scanning increased uptake was noted in 49/119 patients (39%)
- Uptake seemed to parallel RA disease activity
- Question
  - What impact does this finding have on heart disease and heart failure?

<https://onlinelibrary.wiley.com/doi/10.1002/art.40771>



# Rheumatoid Arthritis

## Gut bacteria and RA

- “Hey Doc, antibiotics make my arthritis better”
- We know that there exists a link between periodontitis and RA likely through two pathogens
  - *Aggregatibacter actinomycetemcomitans*
  - *Porphyromonas gingivalis*
- There may be other bacteria pathogens as well with *Prevotella capri*
  - Impacts the balance with *Bacteriodes*
- These research findings may eventually lead to the link of mucosal injury and autoimmunity and impact treatment choices
- The Rheumatologist, 2019. <https://www.the-rheumatologist.org/article/links-between-gut-bacteria-and-rheumatoid-arthritis/4/>



# Rheumatoid Arthritis

## Check Point Inhibitors

- Check point inhibitors are used widely in oncology care. Two commonly targeted checkpoints include:
  - CTLA-4
  - PD-1
    - Blockage enhances T cell function and tumor lysis
- These drugs are associated with immune-related adverse events from self tolerance
- Myalgia/arthralgia, GI, skins, hepatic, and endocrine system abnormalities have all been described
- May require immunosuppressants to treat
- The Rheumatologist, 2018. <https://www.the-rheumatologist.org/article/immune-checkpoint-inhibitors-immune-related-adverse-events/?singlepage=1>



# Systemic Lupus

## Toll Like Receptors (TLR)

- Toll-like receptors are important immune surveillance.
- TLR-7 has been implicated in the pathogenesis of lupus and more recently so has TLR-9 (Celhar, et al., Arthritis Rheumatol. 2018).
- In the case of TLR-9, disease is the result of ablation.
  - The result of research in TLR-9 deficient mice
- This study supports the importance of bench research colleagues in the development of new novel therapies
- The Rheumatologist, 2019. <https://www.the-rheumatologist.org/article/in-mouse-model-a-tlr-9-deficiency-may-trigger-severe-lupus/?singlepage=1>



# Systemic Lupus

## Depression

- We all know that depression is often seen in patients with chronic illness
- This study suggested that depression may be a risk factor for the development of lupus (Roberts, et al., JAMA Psychiatry, 2018)
  - Study used two large cohorts of patients assessed over 20 years
  - Diagnosis used the ACR criteria
- It may be reasonable to spend time asking question about autoimmunity symptoms in your patients with depression.
- <https://www.ncbi.nlm.nih.gov/pubmed/30208373>



# Systemic Lupus

## Cardiovascular risks

- Patient with lupus have a higher incidence of CV risk factors despite their female sex and lower age prevalence
- Research has demonstrated that these patient have less screening and treatment for these risk factors (Chen, et al., Arthritis Care & Research, 2019)
  - These patients also have less statin prescriptions
- The Rheumatologist, 2019. <https://www.the-rheumatologist.org/article/sle-patients-may-not-receive-enough-cardiovascular-disease-assessment-treatment/?singlepage=1>



# Systemic Lupus

## ANA Testing

- ANA testing is a constant source of aggravation
- Researchers took sera from patients with lupus and analyzed their sera on three commercially available kits (Pisetsky, et al., Ann Rheum Dis., 2018)
  - Poor overall correlation especially with the ELISA kits
  - Suggested one of the two approaches
    - ELISA or multiplex for screening followed by an ANA by IFA
    - Start with the ANA by IFA and then a multiplex to assess for other antibody positivity.

<https://www.ncbi.nlm.nih.gov/pubmed/29440000>

The Rheumatologist, 2018. <https://www.the-rheumatologist.org/article/new-study-reveals-limitations-in-ana-test-kits-for-lupus/?singlepage=1>



# Gout

## Prevalence

- Chen-Xu, et al. reported that the prevalence of gout was 3.9 % in US adults (9.2 million people between 2015-2016)
  - 5.2% in men
  - 2.7% in women
- Hyperuricemia rates were approximately 20% in the same population
  - Rates increase with age
- These rates have remained stable since 2007
- Treatment rate for gout was approximately 33%
- Chen-Xu, et al., Arthritis Rheumatol. 2019
- <https://onlinelibrary.wiley.com/doi/10.1002/art.40807>
- <https://www.the-rheumatologist.org/article/new-study-does-urate-lowering-therapy-reduce-gout-patient-mortality/?singlepage=1>



# Gout

## Allopurinol and renal disease

- Study looked at the risk of CKD and progression in allopurinol users (Vargas-Santos, et al., JAMA Intern Med., 2018)
- Looked at stage 1 and stage 2 CKD
  - Allopurinol 300 mg initiated in newly diagnosed gout
    - Those in the allopurinol group had a 13% lower risk of progressing to stage 3 CKD at a mean follow up of 5 years
    - Smaller allopurinol doses did not have the same impact
- When facing worsening CKD in a gout patient on allopurinol look for other causes
- <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2705694>
- <https://www.the-rheumatologist.org/article/allopurinol-for-gout-an-unlikely-contributor-to-kidney-disease/?singlepage=1>



# Gout

## Febuxostat and cardiovascular risks

- The FDA recently placed a CV warning on febuxostat
- This was the result of a study by White, et al. in the NEJM (2018)
  - 6190 patients received either allopurinol or febuxostat from 32-85 months
  - 56.6% discontinued the trial regimen and 45% discontinued follow up
  - The primary endpoint was a composite of:
    - Cardiovascular death
    - Nonfatal MI
    - Nonfatal stroke
    - Unstable angina with urgent revascularization



# Gout

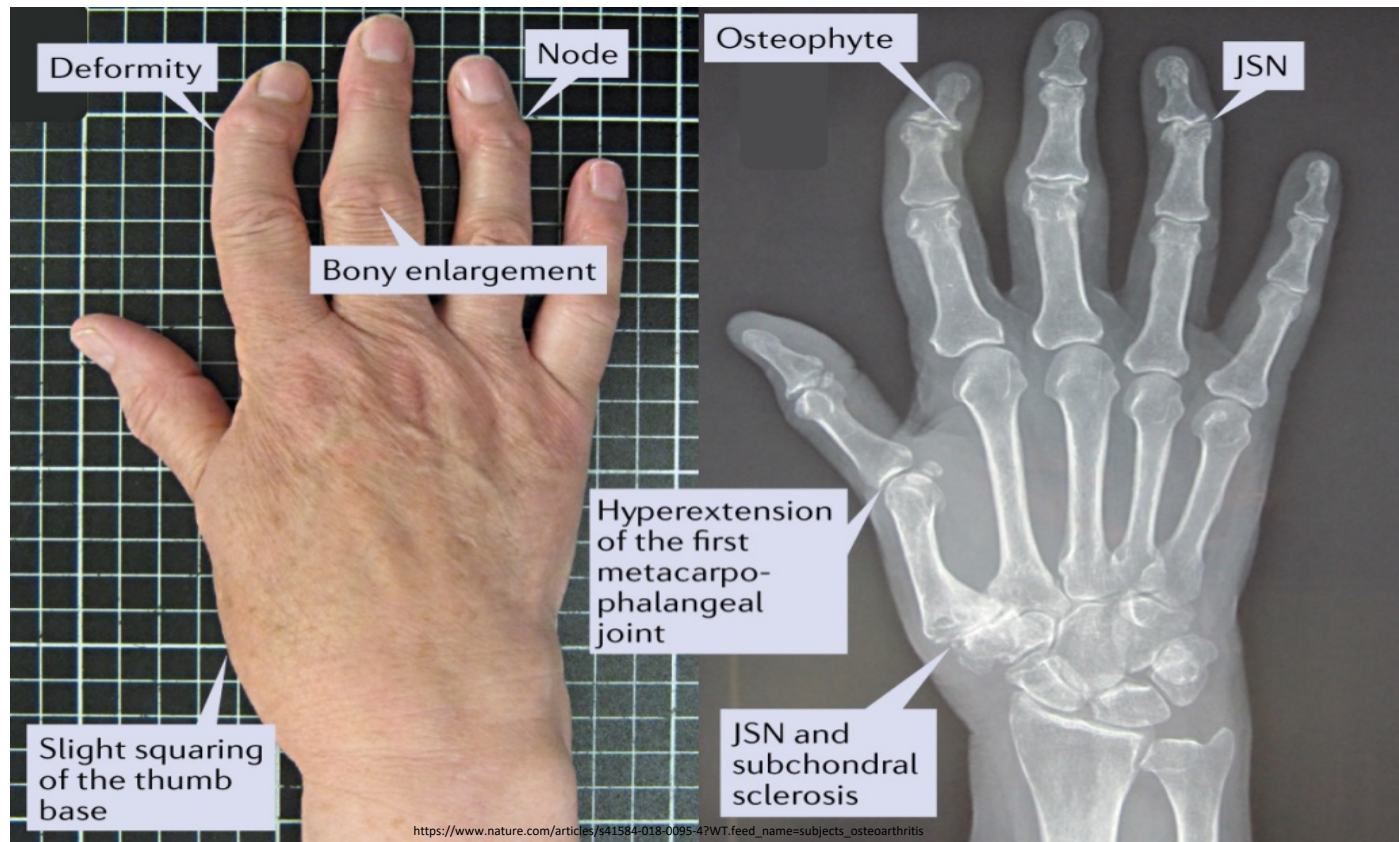
## Febuxostat and cardiovascular risks

- The primary endpoint composite score was:
  - 10.8% in the febuxostat arm
  - 10.4% in the allopurinol arm
- A pre-specified analysis of all-cause mortality and CV mortality demonstrated:
  - A hazard ratio for CV death of 1.34 (CI 1.03-1.73) in the febuxostat arm
- Discuss CV issues with patients and preferentially use allopurinol
- <https://www.ncbi.nlm.nih.gov/pubmed/29527974>
- <https://www.the-rheumatologist.org/article/new-study-raises-cardiovascular-questions-about-febuxostat-for-gout/?singlepage=1>
- <https://www.the-rheumatologist.org/article/study-finds-newer-gout-drug-poses-risk-heart-patients/?singlepage=1>



# Erosive OA

## Treatment options



# Erosive OA

## Treatment options

- Symptomatically these patient have inflammatory complaints
- European League Against Rheumatism (EULAR) guidelines suggest:
  - Focus is on symptomatic therapy and not anti-inflammatory therapy
  - Avoid systemic therapy. Instead try:
    - Topical NSAIDs
    - Splints
    - There is a role for limited joint injections
    - There is a role for Chondroitin sulfate



# Erosive OA

## Treatment options

- I personally have used DMARDs though the data is slim to none.
  - Hydroxychloroquine
  - Minocycline
  - methotrexate
- Recent study looked at the use of etanercept for erosive OA with swollen joints and found no symptomatic improvement after 24 weeks
  - Kloppenburg, et al., Ann Rheum Dis., 2018
  - <https://ard.bmj.com/content/early/2018/10/03/annrheumdis-2018-213202>



# Knee OA

## Novel therapy

- To date, like other forms of OA, treatments remains symptomatic
- Injection therapy includes both steroids and hyaluronic derivatives
- Some are pushing “stem cell therapy”
- Editorial to follow:
  - We are not talking about multipotent stromal cells from the bone marrow or umbilical cord blood and we are not talking about embryonic stem cells
  - Expensive
  - Not covered by insurance
  - Not proven



# Knee OA

## Novel therapy

- Yazici, et al., Osteoarthritis Cartilage, 2017, looked at the utility of an injectable small molecule which a Wnt pathway inhibitor
  - Demonstrated symptomatic improvement for up to 12 months
  - <https://www.ncbi.nlm.nih.gov/pubmed/28711582>
  - <https://acrabstracts.org/abstract/efficacy-and-safety-from-a-phase-2b-trial-of-sm04690-a-novel-intra-articular-wnt-pathway-inhibitor-for-the-treatment-of-osteoarthritis-of-the-knee/>
- Other are looking at gene therapy, which has been explored and found to be effective in large and small animals
  - Nixon, et al., Arthritis Rheumatol., 2018
  - <https://onlinelibrary.wiley.com/doi/10.1002/art.40668>



# ACR guidelines

## Reproductive issues and medications

- The ACR guidelines are in review currently though excerpts were presented at the 2018 National meeting.
- Men trying to conceive:
  - Discontinue cyclophosphamide 12 weeks before and thalidomide four weeks before attempting to conceive
  - Continue hydroxychloroquine, colchicine, azathioprine, TNF inhibitors, sulfasalazine, methotrexate, leflunomide, mycophenolate, cyclosporine, tacrolimus, anakinra and rituximab
  - Consider semen analysis if a man has trouble conceiving while on sulfasalazine
    - SAZ can be associated with reversible fertility issues



# ACR guidelines

## Reproductive issues and medications

- Women trying to conceive or become pregnant:
  - Medications to stop during pregnancy:
    - cyclophosphamide, thalidomide, mycophenolate, methotrexate and leflunomide,
    - ANY previous leflunomide should prompt a “wash out” before pregnancy and immediately if pregnant
  - Avoid NSAIDs in the third trimester
  - Medications that may be continued during pregnancy:
    - hydroxychloroquine, sulfasalazine, and azathioprine
    - Continue TNF-inhibitors during pregnancy if clinically necessary
      - Be aware of data of using live vaccines with caution, for one year, in babies born to mothers who used anti-TNF therapy during pregnancy
    - Low dose non-fluorinated steroid therapy if needed
- I often use high risk OB for pregnancy planning



# Cannabis

## Terminology

- **Cannabis**—The scientific and historical name for the tall, bushy, fast-growing, cane like weed used as a drug by humans for thousands of years. The female unfertilized flower buds are the most potent.
- **Cannabinoids**- The active ingredients in marijuana, like THC and CBD; there are about 60-100 cannabinoids.
- **CBD- Cannabidiol** – the second most common active ingredient in cannabis . Does not cause euphoria and may be a powerful anti-inflammatory, antispasmodic and antianxiety drug.
- **THC**- Tetrahydrocannabinol- the main active ingredient in marijuana. Isolated in 1967. It causes euphoria. Most research on medical efficacy for pain, nausea and spasms comes from studies with THC.
  - Hemp which is less than 0.3% THC/20%+ CBD
  - Marijuana which is more than 20% THC/10%+CBD



# Cannabis

## Terminology

- Terpenes are common, often aromatic, organic compounds found in many plants.
  - Cannabis plants have over 120 identified terpenes with different aromas.
  - There may be an association with psychoactive effects for strains and smells.
  - They reduce the intoxicating effects of THC when consumed together and add additional therapeutic value.



# Cannabis

## Terminology

- Two types of hemp oil –
  - one is pressed from the hemp stalks
  - one is from the seeds
- Hempseed oil (oil pressed from the seeds) has been used for years and is used as a moisturizer in many beauty products - Hempseed oil is listed as a cannabis sativa seed oil
- **CBD only oil comes from Hemp extract. (<0.3% THC) also called Hemp Oil**
- **Cannabis oil would contain CBD, THC and terpenes**
- This matters because the CBD oil is more expensive and has a variety of legal ramifications



# Cannabis

## Concentrate types

- Tinctures
- Topicals
- Capsules
- Vaporizers
- Many types of edibles.
- The cannabis of the 60's and 70's had maybe at most 4% THC
- Some products now tested have ranges of 20% to 45% THC with little CBD content
- CBD products are not federally regulated
  - May not be any CBD in CBD oils
  - Possibility of multiple contaminants



# Cannabis

## Prevalence

- Rheumatic disease registry (FORWARD) patients asked if they had ever used marijuana, cannabis or cannabidiol (CBD)
- Among 11,006 respondents the prevalence of past or current cannabis use has increased from 6.3% in 2014 to 17.6% in 2019
- At both time points, patients reporting use were younger, had worse measures on all PROs and were likely to have a history of smoking cigarettes , have fibromyalgia, report a history of depression and report opioid use



# Cannabis

## Legality issues in Nebraska



- 1 of 3 States where marijuana is illegal
- **Fact 1** - If a police officer catches you buying, possessing or smoking pot, it is a ticket or a jail sentence
- **Fact 2** - If you buy hemp seed oil in a store there will be **no legal action**
- **Fact 3** - There is much confusion of what to do with CBD or cannabidiol oil
- State Attorney General states that CBD is illegal
- Douglas County Attorney states that his law enforcement officers will not target businesses selling CBD products
- The Nebraska Farming Act - LB657 - allows industrial hemp to be grown in Nebraska
  - 10 groups have received the go ahead
  - There were 176 requests
- Problem - How to tell how much CBD or THC is in the hemp plants without labs in Nebraska testing

Slides: Courtesy of Michelene Heath-Holmes, MD



# Rheuminations

Closing thoughts and Questions





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