Autoimmune Disease Treatments Beyond The Basics

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Rheumatology
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Disclosures

- Adult health only-13 years and older
  - No pediatric experience
- Garden hose/garden fire analogies from Dr. Robin Hovis, MD

Rheumatology Related Issues

- **Arthritis**
  - Inflammatory – Rheumatoid arthritis and Spondyloarthropathies
    - *Rheumatoid arthritis*-an autoimmune disease that can cause joint pain and damage throughout the body
      - Mainly affects peripheral joints, 1% of population, cause unknown
    - *Spondyloarthropathies*-long term inflammatory disease of joints
      - More affect on axial joints (spine)
        - » Undifferentiated-variety of symptoms that cannot be classified
        - » Ankylosing Spondylitis-affecting spine and overtime can fuse vertebrae
        - » Psoriatic Arthritis-inflammatory arthritis similar to RA in those that have psoriasis
        - » Reactive Arthritis -usually occurs after infection (i.e. STD, food poisoning, etc.)
        - » Enteropathic Arthritis (ulcerative colitis & Crohn's)
- **Systemic Lupus Erythematous**-immune system attacks its own tissues
- **Sjogrens**-dry eyes, dry mouth
- **Scleroderma**-hardening and tightening of skin and connective tissues
- **Polymyalgia Rheumatica**-inflammatory disorder causing muscle pain and stiffness
- **Vasculitis**-inflammation of blood vessels throughout the body
- **Polymyositis/Dermatomyositis**-rare disease that causes muscle inflammation and skin rash
- **Behcets**-inflammation of blood vessels affecting mouth, eyes, skin and genital areas
- **Gout**-elevated levels of uric acid crystallizing in joints
- **Fibromyalgia**-wide spread pain throughout the body for at least 3 months

Diagnosis- Inflammatory vs. Non-inflammatory

Non-inflammatory Disorders
OA

- Very little to no morning stiffness
- No constitutional symptoms
- Most bothersome after periods of prolonged *activity/use*
- Most often unilateral but sometimes symmetrical (knees)
- No synovitis present
- No multisystem involvement
- No lab abnormalities

Inflammatory Disorders
RA, PsA, lupus, etc.

- Prolonged morning stiffness
- Constitutional symptoms present (fever, fatigue, headache, myalgia)
- Most bothersome after periods of *non-use/inactivity*
- Most often symmetrical joints
- Synovitis present
- Multisystem involvement often
- Lab abnormalities present

Diagnosis-
Systemic Lupus Erythematosus
(SOAP BRAIN MD)

- **S**erositis
  - Pleuritis or pericarditis
- **O**ral ulcers
- **A**rthritis
  - Synovitis specifically
- **P**hotosensitivity

- **M**alar rash
- **D**iscoid rash

- **B**lood/Hematologic disorder;
  - hemolytic anemia, leukopenia, lymphopenia or thrombocytopenia
- **R**enal disorder
  - proteinuria >0.5gm/24 hour or 3+ dipstick
- **A**ntinuclear antibody positive
- **I**mmunologic disorders
  - elevated DsDNA
  - +Anti-Sm Ab
  - low C3/C4 and/or abnormal CH50
- **N**eurological disorder
  - seizures or psychosis

Diagnosis
Lupus cont.

- Classification criteria is objective
  - need four or more of eleven criteria to dx SLE
- Symptoms reported by patient alone- (arthralgias, malaise, fatigue) in absence of objective data do NOT mean Lupus
- A positive ANA does NOT mean Lupus
  - secondary testing needed

Poor Prognostic Factors

- Persistently or moderately high disease activity
- Elevated CRP
- High swollen joint count
- Presence of significantly elevated RF and/or Anti-CCP testing
- Presence of early erosions
  - x-rays of hands and feet
- Failure of 2 or more DMARDs

DIAGNOSIS-
Polymyalgia Rheumatica (PMR)

- Age >65
- Sudden onset joint pain and stiffness in shoulders, upper arms, hips, thighs, neck and/or torso
- Elevated ESR >40
- Great response to Prednisone
- Typically runs its course in 6months-2years

Diagnosis-Fibromyalgia

- Fibromyalgia Diagnosis-widespread pain throughout the body for at least 3 months or more
- Criteria needed- pain in at least 4 of 5 areas:
  - Left upper region-shoulder, arm or jaw
  - Right upper region-shoulder arm or jaw
  - Left lower region-hip, buttock or leg
  - Right lower region-hip buttock or leg
  - Axial region-neck, back, chest or abdomen
- Complete H&P
  - No synovitis
  - Positive tenderpoints/bursitis/tendinitis
    - NOTE-18 tenderpoint exam not required
  - Negative serology (i.e. CBC, ESR, Anti-CCP, RF, TSH, ANA, celiac testing, Vitamin D). Diagnosis of exclusion
  - Sleep apnea testing
  - Trauma/mental health history

Medication Therapies

- NSAIDs
- DMARDS
- JAK-I
- Otezla
- Biologics
- Corticosteroids
- Fibromyalgia specific medications

NSAIDs

- OTC-ibuprofen, motrin, aleve, naproxen
- Rx-Celebrex, Relafen, Sulindac, Meloxicam, Daypro
- Pulled off market-Bextra, Vioxx
- Major side effects: GI upset, ulcers, kidney and liver damage, HTN, fluid retention
  - Celebrex often easier on stomach but still increases BP
- Like a garden hose, on a garden fire, these drugs are very helpful if “fire” is not too big, but quickly lose effectiveness if “fire” is too big. Changing “type” of garden hose seldom makes a big difference.

DMARDs

- **D**isease **M**odifying **A**nti-**R**heumatic **D**rug**s**
  - Methotrexate (Trexall)
  - Hydroxychloroquine (Plaquenil)
  - Leflunomide (Arava)
  - Sulfasalazine (Azulfidine)
  - Azathioprine (Imuran)
- Mechanism Of Action
  - Inhibits the immune responses of monocytes and of T and B lymphocytes. Many inhibit responses to, or production of, cytokines.
  - DMARDs tend to differ in their therapeutic efficacy in individual patients for unknown reasons (hence the 'trial and error' frustration with patients)
- Helpful Hints
  - Have been used for many years and providers are very familiar with them
  - Minimize joint damage
  - Dual therapy with mtx typically works quite well
  - Typically cheap (Good Rx and like programs work well with these)

Methotrexate

- Like a fire truck on a garden fire-more powerful weapon against “fire”.
  - Before mtx ½ of patients were on disability within 2 years. Now average is 10 years.
- Oral or injection weekly dosing
- *Disadvantages:*
  - Takes time to work
  - Very toxic to fetus’-avoid in women who may get pregnant
  - MUST avoid ETOH
  - Side effects range from mild to toxic including; nausea, mouth sores, fatigue, blood count abnormalities and lung inflammation/scarring (fibrosis)
  - Need frequent lab monitoring.
- *Advantages:*
  - *Usually very effective for any type of rheumatological condition*
  - Good long term safety data
  - Can combine with other meds for dual therapy
- Most common reason for SE of mtx (nausea, stomach pain, stomatitis, anemia) results from medication inhibition of folate acid metabolism.
  - Folic acid 1mg daily

Hydroxychloroquine (Plaquenil)

- Mild drug, mild side effects, often not strong enough
- Weight based dosing 5mg/kg
- Short term SE: minimal nausea, diarrhea, rash
- Long term SE: small risk retinal toxicity at 4-6 years. Need annual VFT (visual field testing)

Sulfasalazine

- *Advantages:*
  - Good long term safety data
  - Low risk to fetus
  - Relatively cheap
  - Rarely causes toxic side effects
- *Disadvantages:*
  - Alcohol does alter risk to liver
  - Side effects range from diarrhea to rash (common)
    - Do not use if known sulfa allergy

Leflunomide (Arava)

- *Advantages:*
  - Oral
  - Generally affordable
  - Works well in dual therapy with mtx
- *Disadvantages:*
  - Side effects include diarrhea (#1), nausea
  - Can affect blood counts and liver
    - Alcohol increases risk of issues with liver
  - Fetal abnormalities
  - Very long half life, can be removed faster with administration of cholestyramine.

GOLD Tx and Penicillamine

- Historical interest mainly
  - Too toxic for most patients
  - More than 1/3 had moderate to severe toxicity
    - Some side effects not reversible
    - Many severe side effects were not predictable

Complicated Lupus Specific Treatments

- Azathioprine (Imuran), Cyclophosmamide (Cytoxan), Cellcept (Mycophenolate)
  - In certaion cases can also treat systemic sclerosis (scleroderma), some forms of vasculitis, polymyositis and dermatomyositis; and sometimes rheumatoid arthritis.
- VERY potent anti-inflammatory and immunosuppresant
  - Increases risk of malignancy
  - Not safe in pregancy
  - Much higher risk of toxic effects

Imuran

- Used to treat lupus affecting liver and kidneys
- **T**hio**p**urine **methyltransferase** (TPMT) is an enzyme that breaks down (metabolizes) a class of drugs called thiopurines. Used to assess tolerance to med
- Steroid sparing-can lower steroid dose in most cases
- Oral, takes 6-12 weeks to work
- SE: stomach and blood cells
  - Take with food
  - Get regular lab tests
- DO NOT take with allopurinol, coumadin, ACEI, sulfasalazine, olsalazine, mesalamine

Cellcept

- Used to treat lupus with renal involvement
- Steroid sparing
- BID dosing and multiple pills
- SE: N/V/D, dizziness, sleeplessness, tremors, low WBC
- Wear sunscreen
- DO NOT take with questran, acyclovir, gancyclovir, imuran, antacids, oral contraceptives, bactrim, theophylline, dilantin, ASA

Cytoxan

- Used to treat very severe cases of lupus with multi-organ involvement.
- Given mainly by IV as SE worsen with taken orally
- Many side effects
- DO NOT take with allopurinol, phenobarbital, coumadin, thiazide diuretics, herbal supplements and some psych meds

Benlysta

- Approved to treat complicated lupus (2011)/lupus nephritis (2020)
- monoclonal antibody specific for B lymphocyte
- Used with other lupus meds
- Given IV or SQ
- Many side effects
- Expensive

Targeted small molecule DMARD
JAK-I

- **Ja**nus **K**inase **I**nhibitors (JAK-I)
  - Baricitinib (Olumiant)
  - Tofacitinib (Xeljanz)
  - Upadacitinib (Rinvoq)
- Mechanism Of Action:
  - *BASIC*: With RA, the body makes too many proteins called cytokines, which play a role in inflammation. Some cytokines attach to receptors on immune cells (like a key fitting into a lock). When that happens, messages are sent to the cell to make even more cytokines (which opens the door). JAK-I put a wrench in the process (closes the door) by blocking the messaging pathway which calms down the immune system (the key is removed).
  - *ADVANCED*: Work in association with type I and II cytokine receptors, which are intrinsic elements of immune responses. Consequently, inhibiting these enzymes has great potential for controlling unwanted or overactive immune pathways such as in RA.
- Advantages:
  - Oral pill, avoids injectables
  - Short half-lives *should* equate with briefer peri-operative interruption compared to biologics and more rapid reversal of adverse side effects
  - Efficacy is at least equivalent to biologics
- Disadvantages:
  - Some of the major cytokines involved in RA pathogenesis, specifically TNF-α, IL-1 and IL-17, are *not* dependent on JAKs for their signaling
  - Cost-more expensive
  - September 2021 new FDA black box warning

JAK-I Black Box Warning September 2021

- After a review of a large randomized safety clinical trial, the FDA said it "concluded there is an increased risk of serious heart-related events such as heart attack or stroke, blood clots, and death with the arthritis and ulcerative colitis medicines Xeljanz and Xeljanz XR (tofacitinib)."
- This trial compared Xeljanz with tumor necrosis factor (TNF) inhibitors (Enbrel, Humira) in patients with rheumatoid arthritis, and results showed an increased risk of blood clots and death with Xeljanz
- This is the third set of warnings for certain Janus kinase (JAK) inhibitors due to this concern
- As a result of the latest finding, the FDA said it would require 2 other JAK inhibitors, baricitinib (Olumiant) and upadacitinib (Rinvoq), to carry the same warning. Although these 2 medicines were not studied in a safety trial similar to Xeljanz, the FDA said it considers the risks to be similar due to shared mechanisms of action

- Source: https://www.fda.gov/drugs/drug-safety-and-availability

Targeted DMARD PDE4 Inhibitor **Otezla**

- Treats:
  - PsA, Behcets (only med FDA approved for such)
- Mechanism Of Action:
  - works inside inflammatory cells to reduce PDE4 activity. A reduction in PDE4 activity is thought to help reduce the overactive inflammation that happens in people with plaque psoriasis/PsA
- Advantages:
  - Oral medication, avoid injections
- Disadvantages:
  - Side effects-D/N/V seem to go away after a few weeks and greatly reduced with up-titration starter dose pack
  - Black box warning for patients with depression/SI
  - Increased risk for CVD/PVD/CVA/CHF
    - Should use CV risk calculator for ages 40-79 and total chol <320

BIOLOGICS-TNF

- **T**umor **N**ecrosis **F**actor **I**nhibitors (aka TNF-I)
  - Humira (Adalimumab), Enbrel (Etanercept), Cimzia, Simponi (Golimumab), Remicade (Infliximab)
  - Treats: IBD+Psa, RA
- Mechanism Of Action:
  - TNF is an inflammatory protein. TNF inhibitors help stop inflammation via cytotoxicity. Although, full molecular mechanism of action of these agents is still a matter of debate
- Helpful advice:
  - Can be used alone or in combination with other meds such as prednisone, oral DMARDs, NSAIDs, etc.
  - 1/3 of patients with rheumatoid arthritis show inadequate response to TNF agents and there is little guidance on choosing the next treatment
  - Promote vaccinations-influenza, COVID, shingles
  - 7 years of data show no malignancy risk identified

BIOLOGICS-non TNF

- Orencia (Abatacept), Rituxan (Rituximab), Actemra (Tocilizumab)
- Mechanism Of Action:
  - Interact with different kinds of WBCs, such as T cells or B cells, in the immune system. They can also block chemicals called cytokines that cause inflammation
- Often used in patients who fail to respond to TNF agents
- Side effects/risks similar to TNF *with* exception of Orencia which has no black box warning for infections except COPD/lung conditions.

Biologics effectiveness

- **A**merican **C**ollege of **R**heumatology-ACR20, ACR50, ACR70
- The ACR20 is a composite measure defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in three of the following five criteria:
  - patient global assessment
  - physician global assessment
  - functional ability measure [most often Health Assessment Questionnaire (HAQ)] in reference to ADLs
  - Pain scale
  - ESR or CRP
- ACR50 and ACR70 are the same instruments with improvement levels defined as 50% and 70% respectively versus 20% for ACR20.
- 70% ACR20 20% ACR70

- Source: https://eprovide.mapi-trust.org/instruments/american-college-of-rheumatology-20-50-70-criteria

Enbrel

- SQ injection weekly
- Approved for psoriasis, PsA, AS
- May use with oral DMARDs
- Major side effects: infections, injection site reactions

Humira

- Treats: PsA, RA, uveitis, Hidradenitis supperativa
- SQ injection every 2 weeks
- May use with oral DMARDs
- Major side effects: injections, injection site reactions

Remicade (infliximab)

- IV infusion at outpatient infusion center
- Dosing: 3 infusions in first 8 weeks then every 8 weeks
  - Dosing weight based
  - Side effects: infusion reactions, infections

Other medication ‘must-mention’

- Orencia AVOID use in those with COPD/underlying lung issues
- Cimzia safe in pregnancy but all other TNFs no supporting data
- OTIS voluntary registry-**O**rganization of **T**eratology **I**nformation **S**pecialists
  - Non-profit organization that assess’ and evaluates risks to pregnancy and breastfeeding outcomes from medications and other exposures. Evidence based. Self referral.
  - Enables informed decision making when discussing treatment options for disease throughout pregnancy and breastfeeding

Biologic categories

TNF

- Humira
- Enbrel
- Remicade/Inflectra
- Cimzia
- Simponi

PDE4 Inhibitor

- Otezla

Non-TNF

- Orencia
- Rituxan
- Actemra

JAK-I

- Xeljanz
- Rinvoq

FDA Approved Uses

	Route	RA	Plaque Psoriasis	PsA	AS	JIA/JRA	Crohn's	UC	Behcets
Orencia	SC,IV	X				X			
Humira	SC	X	X	X	X	X	X	X	
Cimzia	SC	X					X		
Enbrel	SC	X	X	X	X	X			
Simponi	SC	X		X	X				
Remicade	IV	X	X	X	X		X	X	
Rituxan	IV	X							
Actemra	IV	X				X			
Stelera	SC		X						
Xeljanz	Oral	X							
Rinvoq	Oral	X							
Otezla	Oral		X	X					X

Corticosteroids

- Oral
  - Prednisone, Methylprednisolone, decadron
- IM, intra-articular
  - Kenalog, Depo-Medrol
- Great short term treatment but not ideal for long term use
  - Like getting 1” rain per hour on the garden fire. Great short term but if rain keeps up, more damage from rain than from fire.

Prednisone

- Short term: Increases appetite, flushing, jitteriness/difficulty sleeping
  - Take in am
- Long term: diabetes, osteoporosis, thin skin, cataracts, weight gain, hypertension
  - Side effects begin to increase at a cumulative dose of 2,000mg (20mg/day would get you there in 100 days)
- Safe in pregnancy
- Very cheap (<$10/month)

Fibromyalgia Treatment

- Medications:
  - NSAIDs
  - Low–dose tricyclic antidepressants
    - Most commonly used: Amitriptyline and Nortriptyline.
  - Selective serotonin reuptake inhibitors (SSRIs)
    - Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac), Paroxetine (Paxil), Sertraline (Zoloft)
  - selective serotonin and norepinephrine reuptake inhibitors (SNRIs)
    - Duloxetine (Cymbalta), Milnacipran (Savella), Venlafaxine (Effexor)
  - Muscle relaxants
    - Flexeril, Tizanidine, Baclofen
  - Second line treatment: Trazodone, Gabapentin, Lyrica

Fibromyalgia Treatment Cont.

- Other treatment modalities include;
  - Low impact exercise
  - CBT, stress management, counseling
  - Myofascial therapy, PT, yoga, tai-chi
  - Trigger point injections, acupuncture
  - Pain management referral
  - Addressing mental health issues
- OPIOIDS are NOT recommended long term

PsA and co-morbidities

- Very Common
  - Including; ophthalmic disease, depression, fatty liver disease, kidney disease, osteoporosis, CVD, metabolic syndrome, IBD
- Autoimmune ophthalmic diseases
  - Uveitis+PsA: only FDA approved drug is Humira
  - Otherwise; Mtx, Cellcept, Imuran, Remicade
- Depression +PsA
  - Ok to use Humira, Enbrel, Stelara
  - Avoid use of Otezla due to black box warning
- IBD+PsA (celiac, PUD, reflux esophagitis, Chrons, UC)
  - Simponi for UC
  - Cimzia for Crohns
  - Otherwise; sulfasalazine, mtx, steroids, Stelara
  - DO NOT use Cosentyx, Siliq, Taltz as it can make things worse
  - AVOID NSAIDs

COVID and Rheumatology

- Generally hold any rheumatology medication (except fibro tx) during COVID infection
- No specific guidelines on holding meds during vaccination with exception of Rituxan.
  - Rituxan depletes b-cells so concurrent use with vaccination does not allow mounting of antibody response
    - Separate last rituxan infusion by 3 months from vaccination. Can restart within 2-3 weeks.
  - ACR recommends holding mtx 1 week AFTER vaccination but there is no data to support this.

Conclusion

- Several treatment options are available
- Key is to balance side effects and cost with disease activity
- Biologics #1 take away-INFECTIONS
  - UTD vaccinations
- Early treatment = greatest chance of avoiding permanent disability
- Many new meds coming down pipeline (Saphnelo)

QUESTIONS?