

The athlete with arthritis or autoimmune disease

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10.28.23

Disclosures

- I have no relevant financial disclosures

Key references

- <https://ped-rheum.biomedcentral.com/articles/10.1186/s12969-019-0306-9> (2019)
- <https://pubmed.ncbi.nlm.nih.gov/32346802/> (2020)
- <https://www.pnas.org/doi/abs/10.1073/pnas.1705420114> (2017)
- <https://pubmed.ncbi.nlm.nih.gov/36593092/> (2023)
- <https://www.usada.org/spirit-of-sport/education/five-things-know-gluococorticoids/>
- <https://journals.sagepub.com/doi/full/10.1177/23259671231152900> (2023)

Goals

- Discuss likely clinical scenarios those of you caring for athletes may come across regarding arthritis or autoimmune disease
- Discuss clinical features of arthritic or autoimmune conditions which may impact athletic performance and/or safety
- Discuss commonly used medications and their impacts on athletic performance and/or safety

Case #1

- 16 yo female with a 3 yr h/o RF (+) polyarticular JIA treated with etanercept 50 mg/wk, methotrexate 20 mg subq/wk, meloxicam 7.5 mg/d presents to your clinic for a sports physical and clearance to participate in high school soccer. She endorses mild neck and wrist stiffness in the mornings (<30 min), occasional mild dyspepsia, but otherwise feels well. Exam reveals mild synovitis in each wrist with reduced flexion bilaterally but is otherwise normal. How do you proceed?

TABLE**Key characteristics of JIA subtypes: Frequency, age of onset, gender distribution¹¹**

Subtype	% of all cases of JIA ^a	Age of onset	Gender distribution
Enthesitis-related arthritis	3-11	Late childhood and adolescence	Highly predominant in females
Extended oligo-articular arthritis	27-56	Early childhood (peaks at 2-4 y)	Exceedingly predominant in females
Psoriatic arthritis	2-11	Biphasic distribution (early peak at 2-4 y, later peak at 9-11 y)	Predominant in females
Rheumatoid factor-positive polyarthritis	2-7	Late childhood and adolescence	Highly predominant in females
Rheumatoid-factor-negative polyarthritis	11-28	Biphasic distribution (early peak at 2-4 y, later peak at 6-12 y)	Highly predominant in females
Systemic arthritis	4-17	Throughout childhood	Equal
Undifferentiated	11-21	—	—

JIA, juvenile idiopathic arthritis.

^a As variously reported in the literature.

Source: Adapted from Basra HAS, et al. *Br J Radiol.* 2017.¹¹



JIA and sports

- Cochrane review (2008) found no evidence exercise was harmful to children with JIA
 - No increase in JIA flare
 - No improvement (or worsening) in overall well being, functional ability, quality of life
 - <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005954.pub2/full>
- Children with JIA can be successfully placed in progressive exercise regimens and demonstrate improvement in VO₂ max and muscle strength without complications
 - <https://bfpt.springeropen.com/articles/10.1186/s43161-020-00008-6>

JIA and sports

- Children with JIA have VO2 max 21% lower than healthy controls
 - <https://www.jrheum.org/content/29/12/2643.long> (2002)
- Rates of exemption from school sports declined from over 50% in 2000 to under 20% in 2015
 - Higher rates of biologic use, improved functional status, and increasing frequency of inactive disease correlate with higher likelihood of sports participation
 - Increasing age, functional limitation, use of IA steroids, use of PT were associated with higher likelihood of NON-participation in sports
 - <https://ped-rheum.biomedcentral.com/articles/10.1186/s12969-019-0306-9> (2019)

JIA and sports

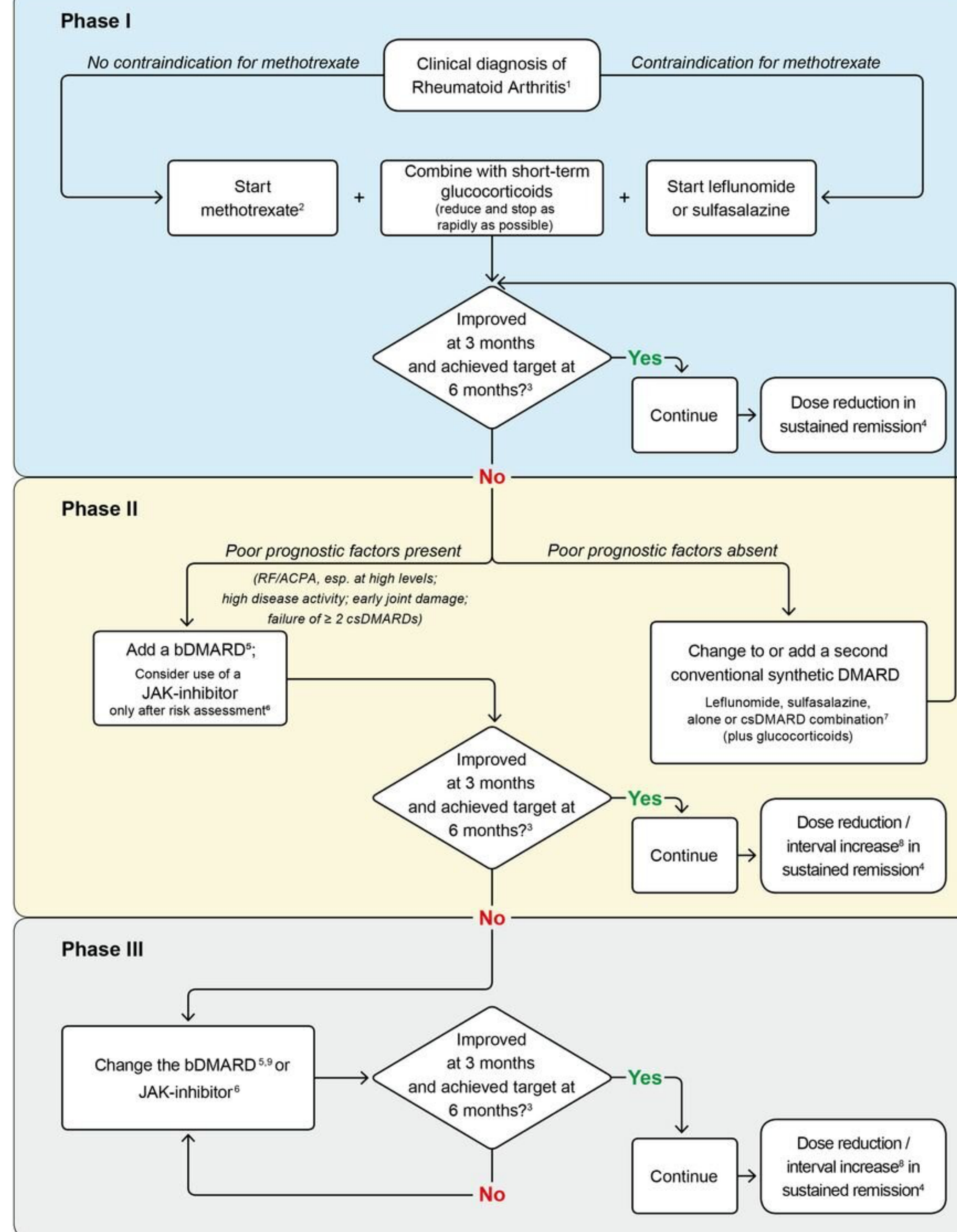
Special considerations

- Cervical spine involvement
- Temporomandibular involvement
- Delayed development and/or muscular imbalances
- PT-based sport-specific prep may be appropriate



DMARDs

- Conventional synthetic DMARDs (disease modifying anti-rheumatic drugs)
 - Methotrexate, sulfasalazine, leflunomide, hydroxychloroquine
- Biologic DMARDs (bDMARDs)
 - Etanercept, adalimumab, infliximab, abatacept, tocilizumab, rituximab, and others!
- Targeted synthetic DMARDs (tsDMARDs)
 - Upatacitinib, tofacitinib, baricitinib



1. 2010 ACR-EULAR classification criteria can support early diagnosis.

2. "Methotrexate should be part of the first treatment strategy". While combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs although more adverse events without added benefit are to be expected, especially if MTX is combined with glucocorticoids.

3. The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be

6. The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other cardiovascular risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated NMSC), risk factors for thromboembolic events (history of MI or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery or immobile)

Any considerations with DMARDs and athletic performance?

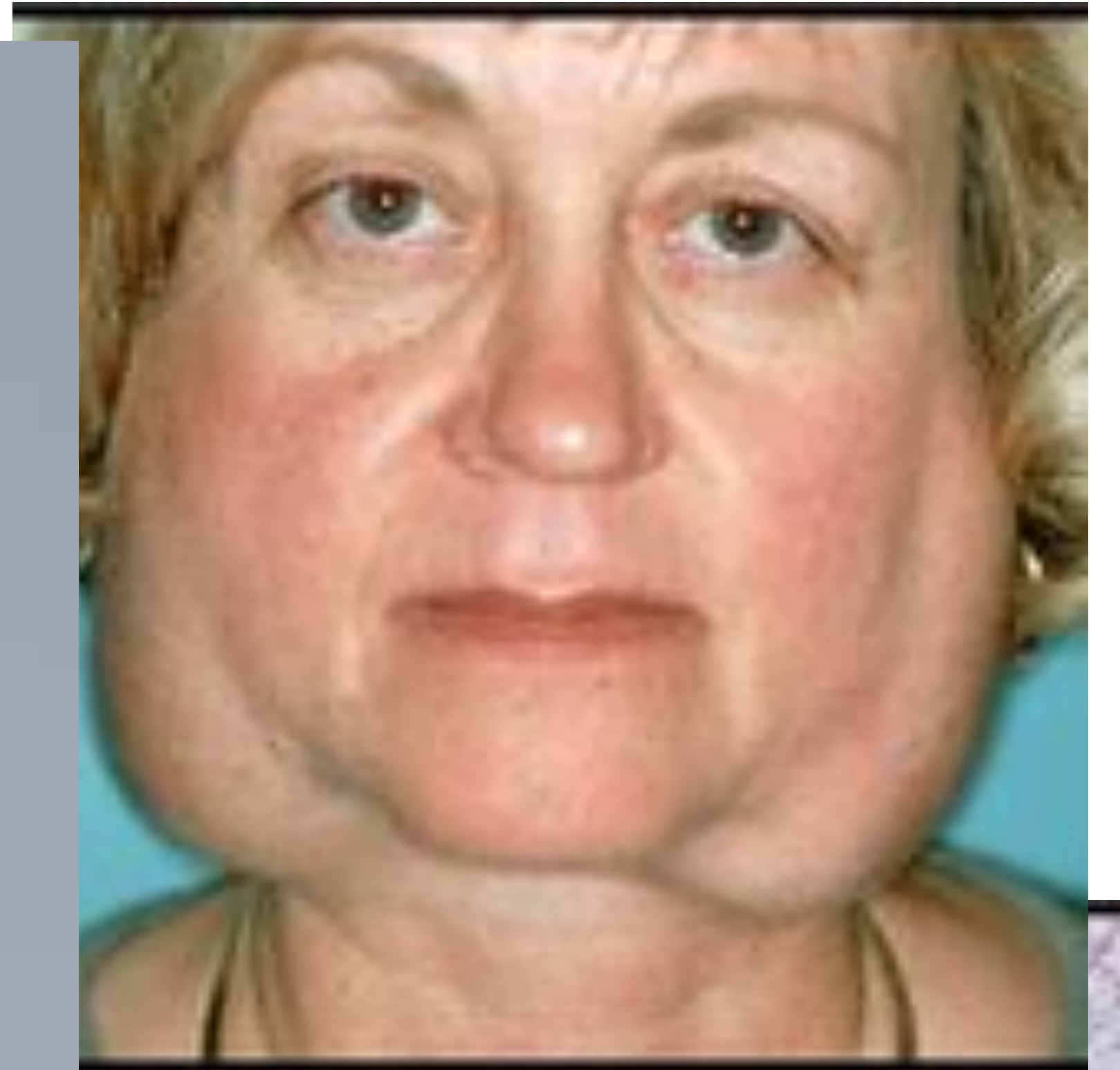
- Methotrexate
 - Photosensitivity
 - Nausea and/or malaise is common 12-36 hrs post-dosing
 - Impaired vaccine responses, potential effects on wound healing
- Hydroxychloroquine, sulfasalazine
 - Nausea, possible photosensitivity
- bDMARDs
 - Immune suppression, no other specific impacts

Any considerations with DMARDs and athletic performance?

- DMARDs vs disease activity
 - (Almost) anything that controls inflammatory disease, is better than inflammatory disease
 - Risks of DMARD therapy, when properly monitored, pale in comparison to risks of under-treated inflammatory disease
 - Increasing rates of sports participation in children with JIA are due to increasing success of DMARD regimens

Case #2

- 25 yo AAF professional tennis player presents with 6 mo h/o gradually increasing fatigue, small joint arthralgia, photosensitivity, a gritty sensation in her eyes and a dry mouth. Physical exam reveals mild bilateral parotid enlargement but is otherwise normal. Labs include WBC 2.5, ESR 95, CRP 0.5 mg/dl, ANA 1:160 homogeneous, SSA >8, RF 25, CCP negative, IgG 4200. She seeks both a diagnosis and a treatment plan that will allow her to continue her professional career. What do you tell her?



Sjogren's syndrome

- Primarily females, middle age
- Dry eye, dry mouth, dry airways, dry skin
- Dry cough, hoarseness, thirst
- Fatigue, arthralgia, rash, neuropathy
- Arthralgia in 96%, inflammatory arthritis in 2-70% (non erosive synovitis, MCPs and other joints, RA-like)
 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8068384/> (2021)
 - <https://images.rheumatology.org/bp/#/folder/8155272/>

Venus's journey (her words)

"No matter how hard I worked, I was exhausted, short of breath, and never felt in shape. It was really frustrating...my symptoms got progressively worse, to the point where I couldn't play professional tennis anymore."

"I literally had professional tennis taken away from me before I got the right diagnosis"

Williams would go to her doctor presenting symptoms, only for her doctors to find nothing medically wrong with her. "I felt out of control," she says.

Williams pulled out of the 2011 U.S. Open when disease-related fatigue became too much to bear

"In the beginning, I just had to wait to get better...one of the medications I had took six months to set in. There was another that took one to three months. It was kind of a waiting game until you can go back to what you had been doing."

"Before I was on medication, the quality of my life wasn't as good because I was extremely uncomfortable...just being alive was very uncomfortable. I was exhausted to the point that I was just always uncomfortable or in pain."

"There are times when things are better and times when they're not as good, that's when you have to listen to your body and understand that...life has changed a little bit, but it doesn't mean that you can't achieve the same things. You just have to be smarter."

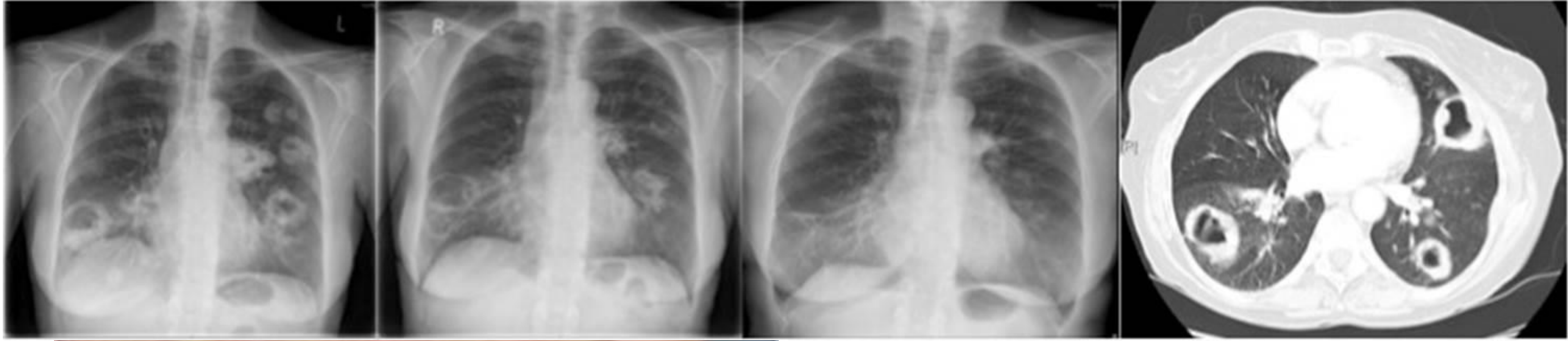
<https://www.prevention.com/health/a28446557/venus-williams-sjogren-syndrome/>

Symptoms of autoimmune diseases

- Fatigue
- Arthralgia, arthritis (often small joint, not otherwise explained)
- Oral ulcers
- Dry eye, dry mouth
- Photosensitive rashes
- Unexplained fever or weight loss
- Pleuritic chest pain, cough, hemoptysis
- Hair loss
- Raynaud's phenomena
- Muscle weakness







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Fatigue and autoimmune disease

- Fatigue is one of the most universal complaints of autoimmune patients
 - 2/3 survey respondents reported fatigue was profound, debilitating, prevented accomplishing routine tasks
 - Neuro-inflammation is implicated, involving Il-1B, TNFa, IL-6, IL-18, IFN- γ
 - Neuro-inflammation has been shown to affect sleep, motivation, anxiety, depression, stress, cognition
 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6691096/> (2019)

Case #3

- 44 yo WM triathlete presents to your clinic for evaluation of right medial ankle pain exacerbated by weight bearing, occurring for the last 2 weeks since a 15 mile run performed in his race flats. Exam reveals mild swelling inferior to the medial malleolus. He has been self-treating with ibuprofen 800 mg TID with mild relief. He is scheduled to race the Ironman world championship in 2 weeks, and questions you about the safety of his NSAID use, the possible role of an oral steroid for acute relief, and how any treatment you offer might affect his ability to race.

NSAIDs

- Older adults (60-85) consuming NSAID (1200 mg/d IBU) had greater strength gain (25-50% over a 12 week program) from resistance training than those not consuming NSAIDs
 - Reductions in IL-6 and MuRf-1 which promote muscle loss
 - PGF2A receptor upregulation increasing skeletal muscle sensitivity to PGF2A resulting in stimulation of protein synthesis. <https://pubmed.ncbi.nlm.nih.gov/21160058/> (2011)
 - Similar results NOT seen in younger subjects (av age 24) but also w lower NSAID dose (400 mg). <https://pubmed.ncbi.nlm.nih.gov/18461099/> (2008)
 - Diclofenac decreases post-exercise muscle injury measured by biopsy and CK rise. <https://pubmed.ncbi.nlm.nih.gov/10912880/> (2000)

NSAIDs

- Meta-analysis of effect of NSAID on sport performance:
 - 23 studies with 500 subjects included
 - No evidence of ergogenic effect of NSAID on sport performance, though studies reviewed were heterogeneous regarding NSAID dose, duration, and type of exercise. “More studies are needed.”
<https://pubmed.ncbi.nlm.nih.gov/32346802/>. (2020)
- Survey of NSAID use in endurance athletes
 - 84% triathletes, 71% runners, 52% cyclists reported NSAID use in prior 12 months, 26% of use was physician advised.
<https://pubmed.ncbi.nlm.nih.gov/30019790/>. (2020)

NSAIDs

- NSAID use in ultra-marathoners
 - 89 subjects, 400 mg IBU q 4h vs placebo, risk of AKI (Cr 1.5x baseline) 52 vs 34% (OR 2.1, 95%CI 0.9-5.1) <https://emj.bmj.com/content/34/10/637> (2017)
- NSAID role in tissue healing and regeneration
 - Prostaglandin E2 (PgE2) is secreted in response to muscle injury, stimulates muscle stem cells (muSC) proliferation, key to myofiber repair
 - EP4 receptor mediates PgE2 stimulating muSC; EP4 knockout mice have impaired muscle repair
 - NSAIDs inhibit PgE2 synthesis
 - <https://www.pnas.org/doi/abs/10.1073/pnas.1705420114> (2017)

NSAIDs

- 14 trained endurance runners (VO₂m 62) ran 36k either pre-treated with 100 mg/d indomethacin or placebo
- Muscle biopsies pre-run and day 1, 3, 8 post-run analyzed for satellite cells (myogenic precursors)
- 27% increase in satellite cells by day 8 post-run in placebo group
- No change in level of satellite cells in NSAID group
- <https://pubmed.ncbi.nlm.nih.gov/17463304/> (2007)

NSAIDs

Comparative efficacy of exercise therapy and oral non-steroidal anti-inflammatory drugs and paracetamol for knee or hip osteoarthritis: a network meta-analysis of randomised controlled trials

- 152 RCTs, 17,431 subjects
- No difference in pain relief between NSAID, paracetamol, exercise at week 4, 8, 24
- No difference in functional improvement at week 4, 8, 24
 - <https://pubmed.ncbi.nlm.nih.gov/36593092/> (2023)

Steroids

- 9 female cyclists rode at 70-75% VO₂max until exhaustion after placebo or 50 mg prednisone/d x 1 week (double blind, randomized, I don't think crossover)
- Cycling time 66.4 +/- 8.4 min vs 47.9 +/- 6.7 min (p<0.001) favoring steroid
 - <https://pubmed.ncbi.nlm.nih.gov/19669785/> (2009)
- Another study in male cyclists found the same, whereas a study of high intensity exercises (single leg hops) found no difference in time to exhaustion (<https://pubmed.ncbi.nlm.nih.gov/24793567/>)
- 9 recreational male cyclists rode 60% VO₂max for 60 min twice, after a single dose prednisone 20 mg or PBO
 - Prednisone intake increased energy expenditure, but reduced CHO oxidation and increased fat oxidation <https://pubmed.ncbi.nlm.nih.gov/17614029/> (2008)

WADA, USADA, TUEs

- World anti-doping association prohibited drug list
 - Classified by “in-competition” and “out-of-competition” with certain washout periods for “out-of-competition”
 - Banned drugs vary by sport (ie, beta-blocker for shooting sports)
 - As of Jan 2022, all oral/injectable/rectal steroids banned in-competition
 - Previous allowance for IA injections
 - All corticosteroids allowed “out-of-competition”
 - In competition=day of, but consider washout period for previous dosing
 - WADA advises 60d washout IM Kenalog, 3d washout oral prednisone
 - Understand role for TUEs (therapeutic use exemptions)
 - <https://www.usada.org/spirit-of-sport/education/five-things-know-glucocorticoids/>

Case #4

- 58 yo WF with a 20 yr h/o seropositive RA as well as moderate bilateral knee OA is treated with upadacitinib 15 mg/d, hydroxychloroquine 400 mg/d, celecoxib 200 mg BID. Her BMI is 35, and due to a new dx of HTN and desire to lose weight, she presents for guidance on the safety of an exercise regimen with her diagnoses. She would like to complete a “couch to 5 k” program with her sister. She usually has mild knee pain when climbing stairs, and a few times/yr a knee or ankle will acutely inflame for a week with an RA flare. Otherwise she feels well. Exam reveals mild bony enlargement to each knee, small effusion left knee, otherwise normal. What do you tell her?

RA and exercise

- Cochrane review of effectiveness and safety of aerobic capacity and/or muscle strength training, land or water based, in RA patients
 - No increase in RA flare or pain
 - Improvements in muscle strength and aerobic capacity demonstrated
 - <https://pubmed.ncbi.nlm.nih.gov/19821388/> (2009)
- 2023 literature review documented numerous studies showing improved physical function, aerobic capacity, sleep, disease activity, clinical severity, and many more domains
 - <https://www.frontiersin.org/articles/10.3389/fimmu.2022.1089621/full> (2023)

Knee OA and exercise

- Systematic review and meta-analysis of running and knee OA
 - 15 studies included
 - OR for surgery related to OA 0.46 (95% CI 0.30-0.71)
 - “Evidence relating to symptomatic outcomes was sparse and inconclusive”
 - <https://pubmed.ncbi.nlm.nih.gov/27519678/> (2017)

Knee OA and exercise

- Systematic review of effect of running on development of knee OA
 - 17 studies, 7194 runners, 6947 non-runners, 55 month followup for runners, 99 months for non-runners, mean age 56 (runners) and 61 (non-runners)
 - Higher knee pain prevalence in non-runners (41% vs 28%, $p < 0.001$)
 - No difference in prevalence of radiographic knee OA or MRI cartilage volume
 - Higher risk of knee OA progressing to TKR in non-runners (4.6%) than runners (2.6%, $p = 0.014$)
 - <https://journals.sagepub.com/doi/full/10.1177/23259671231152900> (2023)

Knee OA and exercise

- Meta-analysis of association between running volume and knee OA
 - 9 observational case control studies, 12,273 participants (1272 runners)
 - No difference in knee OA prevalence runners to non-runners (OR 0.97)
 - Runners of 8-32k/wk, 32-48k/wk, or > 48k/wk had non-significant difference in knee OA prevalence
 - <https://pubmed.ncbi.nlm.nih.gov/36809693/> (2023)

When your athlete asks for a knee injection, just remember...

- 2017 study randomized 70 patients to IA TMC, 70 to PBO every 3 months for 2 years
 - K/L 2/3, U/S evidence of synovitis
 - Mean age 58, 54% women
 - Mean change in index compartment MRI-demonstrated cartilage column -0.21 mm vs -0.10 mm, between group difference -0.11 mm (95% CI -0.20 to -0.03)
 - No significant pain difference (-1.2 vs -1.9 on 0-20 scale, between group diff -0.6, 95%CI -1.6 to 0.3)
 - <https://jamanetwork.com/journals/jama/fullarticle/2626573> (2017)

Case #5

- 17 yo WM basketball player seeks evaluation with one of your trainers due to a cough for several weeks, productive of a small amount of blood today, as well as increasing exercise intolerance during practice. He has been very tired, not eating well, and has lost 5 lbs this month. One knee has been slightly swelled. You order basic labs and a CXR, notable for patchy infiltrates in both lungs, Cr 2.2, HGB 10.5, and urine is notable for 15 RBC, 2+ protein. The state championship is this weekend, and he is your team's starting forward. How do you proceed?

Vasculitis

- Life threatening autoimmune disease will rarely first present to the rheumatologist, and rarely is the first diagnosis to be considered
- Will often affect otherwise healthy patients of any age, as in the case report below
 - https://vc.bridgew.edu/cgi/viewcontent.cgi?article=1019&context=mahpls_fac
(2010)
 - This athlete's short term future will include high dose steroids for several months, a renal biopsy, most likely an infusible chemotherapy (rituximab), and profound immune suppression for the next year or more.
 - With aggressive treatment, he should be able to return to sport though!

Conclusions

- Autoimmune disease affects around 10% of the population (13% females, 7% males) [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(23\)00457-9/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)00457-9/fulltext)
- Healthy level of suspicion, combined with knowledge of symptoms, is needed to identify these patients
- Impacts of diseases and treatments upon athletic performance are present, but can often be mitigated with proper training