RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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Quit Playin' Games with my Heart…

Cardiovascular Considerations with Rheumatoid Arthritis

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Faculty Disclosures

- Janssen Biotech – Speaker, Advisor
- Amgen – Speaker, Advisor
- GSK – Speaker
- Novartis - Advisor

Craig W. Carson, M.D.

- Has hired and trained 23 NP’s and PA’s since 2000
- 20 still working for Oklahoma Arthritis Center, Family Practice Clinic, and Neurology Center.

Cardiovascular Considerations

- Early 1970’s, articles discussing the link between rheumatoid arthritis, and cardiovascular disease started to appear.
- Links between inflammation and heart disease were beginning to be discussed in the 1940’s.

Cardiac Risk and Rheumatoid Arthritis

- Rheumatoid patients have 1.5-2 times increased risk of coronary artery disease compared to the general population.
- It’s about the same as the folks with diabetes
- Experts before a EULAR committee recommended CV risk scores be increased by 1.5 times with people with RA. Yes, 1.5 times.

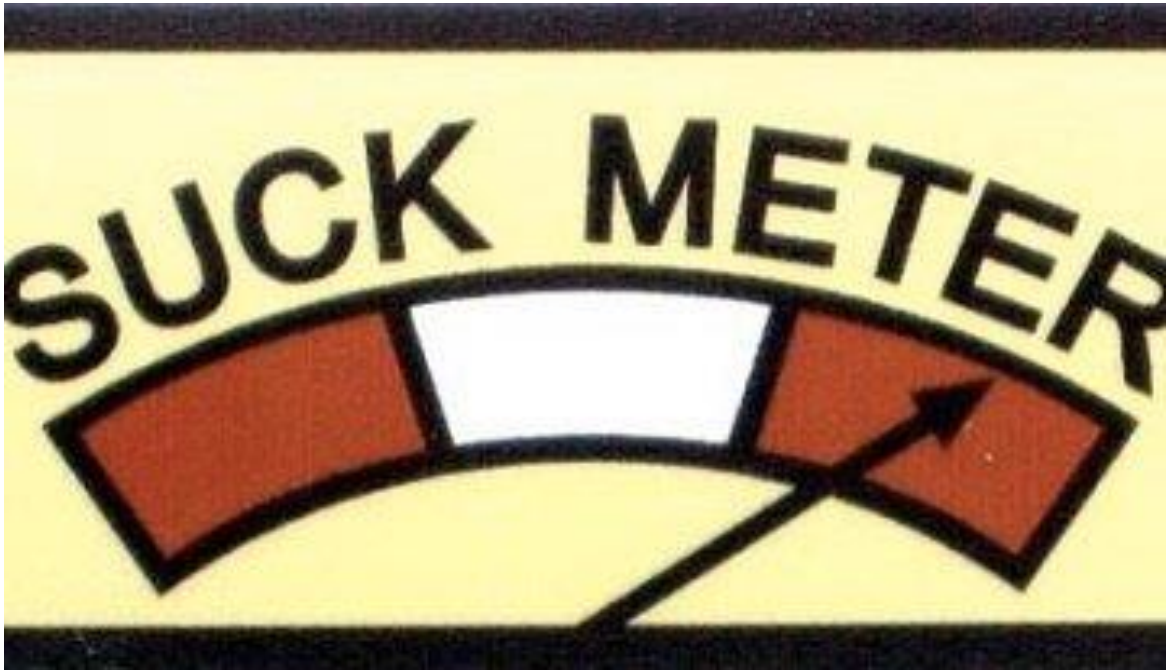
What about heart failure?

- Data is conflicting
- Patients with RA have 2x chance of coming down with heart failure
- RA patients tend to not be treated as aggressively, leading to poorer outcomes.
- Another study showed the opposite, with RA patients more likely to receive thrombolysis and PTCA, and had a 34% improved hospital mortality.

Blood clots…

- Risk of venous thromboembolism appears to be 2-3x increased in rheumatoid arthritis patients, compared to the general population.

Apparently we suck…



We have much to do…

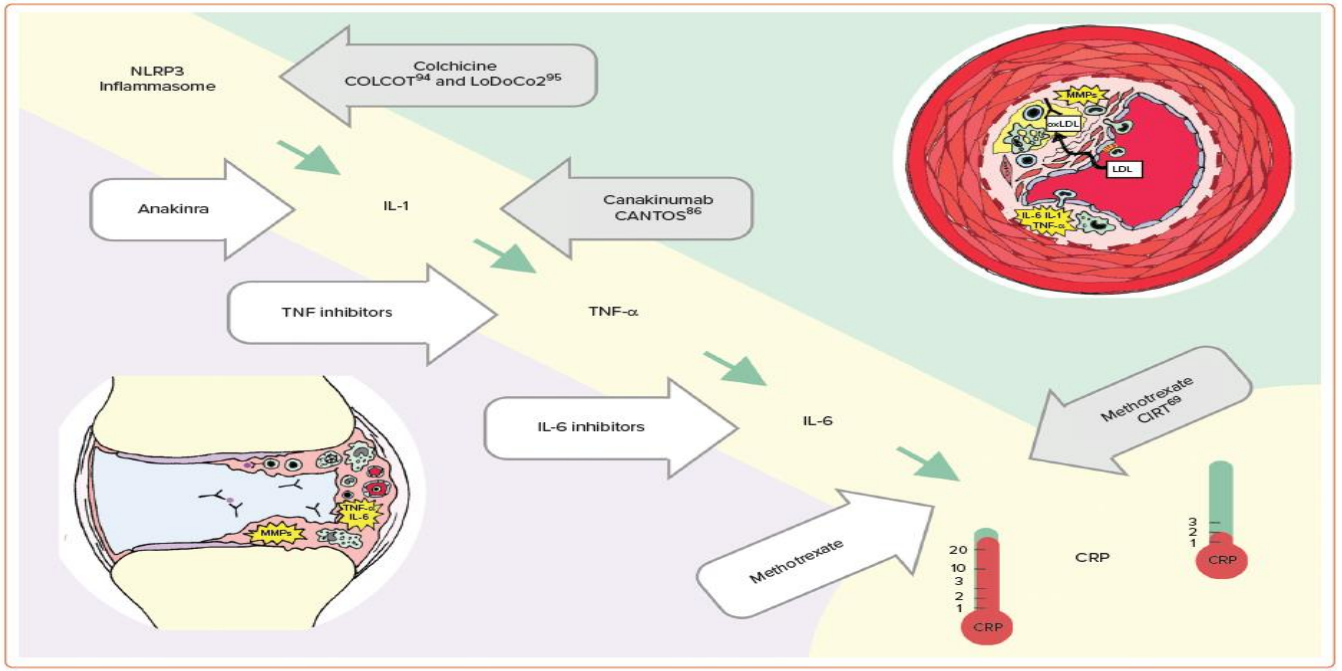
- Rheumatologists are less likely to identify and evaluate cardiovascular risk factors.
- Time has to be a consideration.
- Angina could be underdiagnosed in the rheumatology office… Perhaps we’re writing it off as musculoskeletal, or costochondritis?

Where does this all come from?

- Inflammation appears to be one of the drivers of heart disease
- Other factors are involved, such as tissue hypoxemia, oxidative stress, and endothelial damage.

Inflammation and heart disease

Figure 1: Central Inflammatory Mediators in Rheumatoid Synovitis and Atherosclerosis



NLRP3 inflammasome activates the conversion of pro-IL-1β to biologically active IL-1β. IL-1β promotes production of downstream cytokines TNF-α and IL-6. IL-6 induces hepatic production of acute phase reactants such as CRP. Vascular inflammation in atherosclerosis is usually associated with normal or only slightly increased CRP (low-grade inflammation), whereas active rheumatoid arthritis often results in high-grade systemic inflammation that accelerates atherosclerosis. Antirheumatic drugs that are used to target the central proinflammatory cytokines IL-1, TNF-α and IL-6 are depicted in white arrows, whereas anti-inflammatory therapies that have been investigated in secondary prevention of ASCVD are depicted in grey arrows. ASCVD = atherosclerotic cardiovascular disease; CRP = C-reactive protein; IL = interleukin; LDL = low-density lipoprotein; MMPs = matrix metalloproteinases; NLRP3 = nucleotide-binding oligomerisation domain, leucine-rich repeat and pyrin domain-containing protein 3; oxLDL = oxidised low-density lipoprotein; TNF = tumour necrosis factor.

CAD and T-cells

- Similar changes occur in the hematopoeitic system with RA and coronary artery disease
- Changes in DNA as we age are noted to contribute to myocardial dysfunction in CAD.
- Turns out CD34+ progenitor T-cells have accelerated telomere erosion

CAD and T-cells

- These factors occur both in RA and CAD, and both have been implicated in the pathogenesis of both conditions
- So, it could be that RA and CAD share fundamental pathogenic bases.

The CANTOS Trial

- Canakinumab Anti-inflammatory Thrombosis Outcomes Study
- Canakinumab (Ilaris), an IL-1(beta) antagonist
- Over 10k of patients with a history of MI, and elevated c-reactive protein were given canakinumab 50, 150mg, and 300mg, or placebo, and were observed over an average of 3.7 years.

The CANTOS Trial

- So, over the course of the 3.7 years, cardiovascular events were (in patient-years):
  - 8.4/100 in the 50mg group
  - 8.3/100 in the 150mg group
  - 8.2/100 in the 300mg group
  - 10.4/100 in the placebo group
  - Increased infections, including serious infections, were seen in the treatment groups.

The CANTOS Trial

- Canakinumab did not receive FDA approval, as Novartis asked the FDA for approval for approval of ‘responders’. Meaning, patients whose C-RP’s were driven below 2.0 would be continued on treatment, as this subgroup had much better outcomes.

The CANTOS Trial

- What else can we learn?
- Canakinumab reduced IL-1(beta) and IL-6 levels, as well as c-reactive protein
- Cardiac benefits were modest, but notable, and independent of cholesterol and blood pressure.

The CIRT Trial

- Cardiovascular Inflammation Reduction Study
- Over 6K patients, median run of 2.3 years, with a previous history of multivessel CAD, and/or previous MI.
- Randomized to placebo or MTX 15-20mg/week
- Failed to reduce risk of nonfatal MI, nonfatal stroke, or cardiovascular death

The CIRT Trial

- Stopped for futility, in 2019
- MTX had NO effect on IL-1(beta), or IL-6 levels in the treatment group
- Studies on colchicine are ongoing
- The NLRP3 inflammasome concept is intriguing, as it activates caspase-1.

Recent UK Study

- 81 patients without known CAD were treated with MTX+Enteracept, vs MTX alone
- Cardiac MRI was used to evaluate aortic distensibility
- Although AD improved in both groups, it did not seem to affect CVD outcomes

CAD and Inflammation

- Evidence is compelling, but it doesn’t appear we have a consensus ‘beyond a reasonable doubt…’

Jim

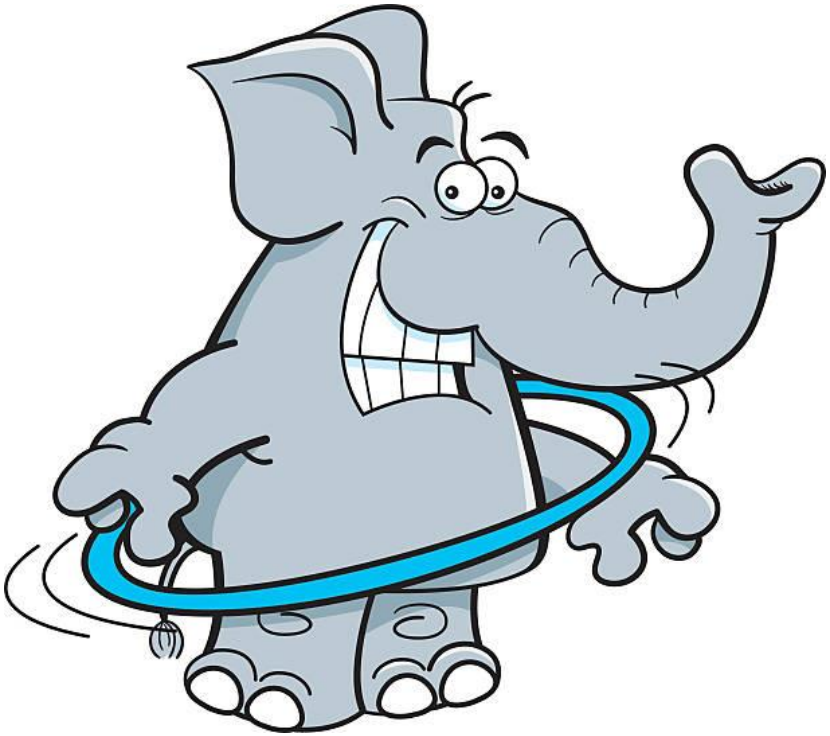
Jim

- 68 year-old all around nice guy
- RA diagnosis for 5 years, stable on MTX and TNF-inhibitor, and as-needed ibuprofen
- Developed chest pain last month, went to ER and found to be having a myocardial infarction
- Got a stent to his LAD (coated)
- Post-MI echo showed no cardiomyopathy

Jim

- How do we address this with Jim?
- Now on Plavix, what medication adjustments need to be made?
- Do we consider changing biologics?

The Elephant in the Room



The Elephant in the Room

- So, what about NSAID’s?
- They can increase risk of hospitalization, as they can contribute to hypervolemia.
- The Vioxx experience
- Animal studies showed Vioxx increase 20-HETE, which can increase vasoconstriction and hypercoagubility.

So, let me explain…

- No, there’s no time. Let me sum up…
- Rheumatoid arthritis and does increase risk of heart disease.
- Our RA patients should be informed of the risks, and screened better
- Risk factors for CAD (Smoking, metabolic syndrome) are also risk factors for RA

RA patients with coexisting CAD

- It’s best to avoid NSAID’s if possible
- JAK inhibitors might not be the best choice
- Avoid TNF inhibitors in moderate to severe CHF
- Improving risk factors for CAD will help RA prognosis.
- Orencia can be considered in CHF.

Questions?

- Thank you!