Top Ten Things Rheumatologists Should (And Might Not) Know About Inflammation and CV Disease

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Recent data have demonstrated an increasingly strong link between chronic inflammatory conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA)/psoriasis, ankylosing spondylitis (AS), and vascular events.[1,2] In addition, atherosclerosis is no longer thought to be a passive disease of lipid sequestration in arteries, but rather an active inflammatory process that appears to share inflammatory and immune pathways with other chronic inflammatory conditions. This article outlines some relevant data regarding the association of chronic inflammatory disease with atherosclerosis and cardiovascular (CV) outcomes.

1. **CV disease is a leading cause of morbidity and mortality in patients with inflammatory arthritis such as RA and PsA.**[1-5] The European League Against Rheumatism (EULAR) guidelines suggest that RA, AS, and PsA should be considered as conditions with a higher risk for CV disease due the presence not only of traditional risk factors but also the burden of inflammatory disease.[2]

2. **The risk of CV events** in patients with inflammatory disease (*e.g.*, RA) is not fully explained by traditional CV risk factors alone.[6,7]

3. **Patients with inflammatory arthritis have a greater burden of abnormalities in surrogate markers of atherosclerosis,** including carotid intimal medial thickness, coronary artery calcium content, and ankle-brachial index as well as abnormalities of endothelial function such as flow mediated dilation, pulse wave analysis, and coronary flow reserve.[8-10]

4. **The pathogenesis of inflammatory arthritis and atherosclerosis share many similarities;** these include T-cell and mast cell activation, production of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-alpha and IL-6, increased expression of leukocyte adhesion molecules, and increased expression of downstream inflammatory markers such as C-reactive protein (CRP).[11,12]

5. **Further linking inflammation and vascular risk,** patients with a higher burden of disease activity appear to be at higher risk for adverse cardiac events compared with patients who have moderate or no disease activity.[13,14]

6. **The lipid paradox seen in inflammatory arthritis**—in which cholesterol appears to be inversely related to CV risk—may be related to the influence of chronic inflammation on lipid values similar to what is seen in a variety of chronic inflammatory diseases as well as in more acute states such as sepsis, cancer, and post myocardial infarction (MI). Notably, suppression of inflammation in RA has been associated with a rise in lipid values but a decrease in vascular risk.[15,16]

7. **Traditional risk factor assessment** (*e.g.*, Framingham Risk Score) may underestimate overall vascular risk as the impact of systemic inflammation is not properly accounted for in traditional algorithms. For example in RA, risk scores should be multiplied by a factor of 1.5 when patients have two of the following:
   - disease longer than 10 years;
   - rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) positivity; or
   - the presence of certain extra-articular manifestations.

   Even with this modification it is recognized that risk may be underestimated. Non-invasive imaging techniques such as carotid ultrasound may be a valuable tool in this setting; having an association with a good cardiac or vascular risk reduction clinic may be valuable.[17-19]

8. **Successful treatment of inflammation with biologic agents has been consistently associated with a decreased risk of CV morbidity.** The EULAR recommendations for CV risk management in inflammatory arthritis[2] suggest that adequate disease control is necessary to lower vascular risk.[20-22]

9. **Atherosclerosis is no longer thought of as a disease of passive sequestration of lipids in the endothelium,** but as an active inflammatory process that involves both the innate and adaptive immune systems and shares many similarities with a variety of chronic inflammatory states such as RA and PsA. Downstream markers of inflammation (*e.g.,* CRP) can give information about an individual's inflammatory state, and are as good as or better than traditional CV risk factors in predicting disease as well as those patients who might benefit from treatment.[23,24]

10. **There are currently two large multicentre trials** testing the hypothesis that suppression of inflammation (utilizing either an IL-1 specific monoclonal antibody[25] or low-dose methotrexate[26]) in patients at high vascular risk may decrease CV outcomes in patients already on optimal medical therapy.

References:

1. Meune C, Touze E, Trinquart L, et al., High risk of clinical cardiovascular events in rheumatoid arthritis: levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. Arch Cardiovasc Dis 2010; 103(4):253-61.
2. Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010; 69(2):325-31.
3. Wong D, Gladman DD, Husted J, et al. Mortality studies in psoriatic arthritis: results from a single outpatient clinic. I. Causes and risk of death. Arthritis Rheum 1997; 40(10):1868-72.
4. Ogdie A, Yu Y, Haynes K, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. Ann Rheum Dis 2015; 74(2):326-32.
5. Horreau C, Pouplard C, Brenaut E, et al. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. J Eur Acad Dermatol Venereol 2013; 27(Suppl 3):12-29.
6. Dessein PH, Joffe BI, Veller MG, et al. Traditional and nontraditional cardiovascular risk factors are associated with atherosclerosis in rheumatoid arthritis. J Rheumatol 2005; 32(3):435-42.
7. Boyer JF, Gourraud PA, Cantagrel A, et al. Traditional cardiovascular risk factors in rheumatoid arthritis: a meta-analysis. Joint Bone Spine 2011; 78(2):179-83.
8. Scarno A, Perrotta FM, Cardini F, et al. Beyond the joint: Subclinical atherosclerosis in rheumatoid arthritis. World J Orthoped 2014; 5(3):328-35.
9. Tam LS, Shang Q, Li EK, et al. Subclinical Carotid Atherosclerosis in Patients with Psoriatic Arthritis. Arthritis Rheum 2008; 59(9):1322-31.
10. Beinsberger J, Heemskerk J, Cosemans J. Chronic arthritis and cardiovascular disease: altered blood parameters give rise to a prothrombotic propensity. Semin Arthritis Rheum 2014; 44(3):345-52.
11. Pasceri V, Yeh ET. A tale of two diseases: atherosclerosis and rheumatoid arthritis. Circulation 1999; 100(21):2124-6.
12. Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? Nat Rev Rheumatol 2015; 11(7):390-400.
13. Libby P. Role of inflammation in atherosclerosis associated with rheumatoid arthritis. Am J Med 2008; 121(10 Suppl 1):S21-31.
14. Solomon DH, Reed GW, Kremer JM, et al. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. Arthritis Rheum 2015; 67(6):1449-55.
15. Myasoedova E, Crowson CS, Kremers HM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of car- diovascular disease. Ann Rheum Dis 2011; 70(3):482-7.
16. Schimmel EK, Yazici Y. Increased lipid levels but un- changed atherogenic index in rheumatoid arthritis patients treated with biologic disease modifying antirheumatic drugs: published experience. Clin Exp Rheumatol 2009; 27(3):446-51.
17. Arts EE, Popa C, Den Broeder AA, et al. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Ann Rheum Dis 2015; 74(4):668-74.
18. Dessein PH, Semb AG. Could cardiovascular disease risk stratification and management in rheumatoid arthritis be enhanced? Ann Rheum Dis 2013; 72(11):1743-6.
19. Gomez-Vaquero C, Robustillo M, Narvaez J, et al. Assessment of cardiovascular risk in rheumatoid arthritis: impact of the new EULAR recommendations on the score cardiovascular risk index. Clin Rheumatol 2012; 31(1):35-9.
20. Westlake SL, Colebatch AN, Baird J, et al. Tumour necrosis factor antagonists and the risk of cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology 2011; 50(3):518-31.
21. Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor alpha therapy and cardiovascular events in rheumatoid arthritis. Arthritis Care Res 2011; 63(4):522-9.
22. Roubille C, Richer V, Starnino T, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Ann Rheum Dis 2015; 74(3):480-9.
23. Libby P, Okamoto Y, Rocha VZ, et al. Inflammation and atherosclerosis: transition from theory to practice. Circ J 2010; 74(2):213-20.
24. Ridker PM, Danielson E, Fonseca FA, et al, for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359(21):2195-207.
25. Cardiovascular Risk Reduction Study (Reduction in Recurrent Major CV Disease Events) (CANTOS). A Randomized, Double-blind, Placebo-controlled, Event Driven Trial of Quarterly Subcutaneous Canakinumab in the Prevention of Recurrent Cardiovascular Events Among Stable Post-Myocardial Infarction Patients With Elevated hsCRP Including Substudies to Evaluate the Effect of Canakinumab on Carotid Atherosclerosis, and on Glucose Control Following OGTT in T2DM. Clinicaltrials.gov; NCT01594333. Available at: *www.clinicaltrials.gov.* Accessed on July 6, 2015.
26. Cardiovascular Inflammation Reduction Trial (CIRT). A Randomized, Double-blind, Placebo-controlled, Event-driven Trial of Weekly Low-dose Methotrexate (LDM) in the Prevention of Cardiovascular Events Among Stable Coronary Artery Disease Patients With Type 2 Diabetes or Metabolic Syndrome. Clinicaltrials.gov; NCT01594333. Available at: *www.clinicaltrials.gov.* Accessed on July 6, 2015.

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