Institutionen för Medicin Huddinge, Enheten för Reumatologi

Addressing cardiovascular risk factors and therapy effects in rheumatoid arthritis: implications for atherosclerosis and cardiovascular disease

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid
Karolinska Institutet offentligen försvaras i sal R64,
Karolinska Universitetssjukhuset Huddinge

Fredagen den 14 december 2012, kl. 09:00

av
Sofia Ajeganova
MD

Huvudhandledare:
Professor Ingiäld Hafström
Karolinska Institutet
Institutionen för Medicin Huddinge
Enheten för reumatologi

Bihandledare:
Professor Johan Frostegård
Karolinska Institutet
Institutionen för Miljömedicin
Enheten för immunologi och kronisk sjukdom

Professor Ulf de Faire
Karolinska Institutet
Institutionen för Miljömedicin
Enheten för kardiovaskulär epidemiologi

Fakultetsopponent:
Professor Lennart Jacobsson
Göteborgs Universitet
Sahlgrenska akademin
Institutionen för Medicin
Avdelningen för reumatologi och
inflammationsforskning

Betygsnämnd:
Professor Ronald van Vollenhoven
Karolinska Institutet
Institutionen för Medicin Solna
Enheten för klinisk behandlingsforskning

Professor Solbritt Rantapää-Dahlquist
Umeå Universitet
Institutionen för Folkhälsa och medicin
Enheten för reumatologi

Docent Nils Feltelius
Karolinska Institutet
Institutionen för Medicin Solna
Enheten för reumatologi

Stockholm 2012

ABSTRACT

Rheumatoid arthritis (RA) is the prototype of chronic inflammatory disease associated with a 1.5-2 fold increased risk of cardiovascular disease (CVD) and premature mortality. Though traditional CVD risk factors are important in the pathogenesis of atherosclerosis in patients with RA, they do not fully explain the increased risk of CVD events observed in RA. This thesis aimed to explore further the mechanisms that could account for accelerated atherogenesis and CVD in RA.

In the study of established RA disease, which included patients treated during one year with TNF-α inhibitors, n=162, or the anti-CD20 agent rituximab, n=53, anti-atherogenic apolipoprotein A1 increased after commencement of therapy; this increase was not agent-specific and paralleled a reduction in RA disease activity. At the same time, apolipoprotein B and the atherogenic index did not change significantly. These favorable effects may have a potential for at least short-term improvement in cardiovascular risk in RA. On the other hand, the biologic agents caused differential effect on serum levels of anti-phosphorylcholine (anti-PC) IgM, a promising atheroprotective biomarker. Thus, these antibodies increased on TNF-α inhibitors in contrast to treatment with rituximab. The contribution of biologic agents to beneficial or harmful CVD effects needs to be elucidated in future studies.

In studies incorporating 114 participants with early RA, examined with high-resolution B-mode ultrasonography after five years of disease, the pro-atherogenic apoB and apoB/apoA1-ratio were independently associated with unfavorable carotid outcomes, while a profitable effect was associated with the anti-atherogenic, anti-inflammatory apoA1. Also, low anti-PC IgM levels longitudinally had an unfavorable association with the plaque presence at the end of observation. These results suggest that apolipoproteins and anti-PC antibodies may have independent roles in subclinical atherosclerosis in patients with RA. Further analysis, over a prolonged observation period more than 10 years, showed that the bilateral carotid plaques occurrence was associated with a subsequent CVD event. Early improvement of inflammation, pain and disability, measured as reductions in DAS28, VAS pain and the HAQ score the first year after RA diagnosis, as well as use of methotrexate were associated with a better CVD outcome. Longitudinal approach confirmed the association of low anti-PC IgM levels and, also, increasing oxidized LDL over first five years of RA disease with an adverse CVD outcome.

In a large observational early RA cohort of 741 patients followed more than 10 years, we examined the relationships of inflammatory and novel biomarkers with incident CVD morbidity and all-cause mortality. The study outcomes were tracked through the Swedish Hospital Discharge and the National Cause of Death Registries. The factors associated with adverse outcomes differed in patients with disease onset before 65 years of old and those 65 years and older. The cumulative burden of inflammation over the first two years and the presence of RA disease related autoantibodies had a value for CVD and mortality prognosis in the younger patients, while a change in inflammatory markers the first year after diagnosis had a stronger effect in the older patients. Low-dose glucocorticoids increased but use of methotrexate decreased risk of poor outcomes in the elderly. These findings imply that age stratification could add to identification of patient-at-risk, and highlight the need to treat RA early and more aggressively to improve long-term outcomes.

Taken together, these results emphasize the complexity of the associations between inflammation, anti-rheumatic therapies, atherosclerotic burden and CVD in RA. Further studies addressing indicators for cardiovascular prognosis are unmet needed.

Key words: rheumatoid arthritis, risk factors, disease measures, carotid atherosclerosis, cardiovascular disease, apolipoproteins, anti-phosphorylcholine antibodies