Dyslipidaemia, statins and rheumatoid arthritis

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CARDIOVASCULAR MORBIDITY AND MORTALITY are enhanced in rheumatoid arthritis (RA) and there is increasing evidence that this is due to the inflammatory process as well as to an increased prevalence of traditional cardiovascular risk factors, such as dyslipidaemia.1–3

DYSLIPIDAEMIA IN ESTABLISHED AND FUTURE PATIENTS WITH RA

Several investigators have indeed demonstrated dyslipidaemia, defined as higher total cholesterol and/or triglycerides and/or lower high-density lipoprotein (HDL) cholesterol levels in comparison to control subjects, in RA and this appears to be the consequence of systemic release of inflammatory cytokines such as tumour necrosis factor (TNF)α, interleukin (IL)1 and IL6, leading to a proatherogenic state with insulin resistance, endothelial cell activation and hypercoagulation as other consequences. The dyslipidaemia in RA is dependent on disease activity, ie, a higher disease activity is associated with lower total cholesterol levels and even more depressed HDL cholesterol levels, leading to a higher (ie, unfavourable) atherogenic index.5

Moreover, it appears that dyslipidaemia is already present in early RA and the question arises whether or not this phenomenon starts in the preclinical phase of RA. Hence, we investigated the lipid profile over time and its relationship with inflammation and serological markers, in subjects who later developed RA.6 The lipid profile was determined in 1078 serial blood bank samples, of 79 blood donors who later developed RA. These samples were compared with 1071 control samples of unselected blood donors, matched for age and sex. The samples of future patients with RA displayed, on average, 4% higher total cholesterol, 9% lower HDL cholesterol and 17% higher triglyceride levels compared to matched controls (p<0.05), at least 10 years before the onset of RA symptoms. Although the differences in the various lipid values were small they may have clinical relevance, in the light of results from other studies. For instance, in a placebo-controlled study with fibrates, the differences of the lipid values between the active treatment and the placebo group were similar to the observed differences in our study and the individuals treated with fibrates had ultimately a more than 20% risk reduction for cardiovascular disease.6

HDL CHOLESTEROL

As the observed differences in lipid levels between future patients with RA and the control subjects were only partially explained by the differences in C-reactive protein (CRP) levels, alternative explanations are required. A tempting idea is that a (marginally) deteriorated lipid profile may render a person more susceptible to inflammation or inflammatory diseases. In other words, one or more of the examined lipids could have a regulatory effect on inflammation. It is well known that contact-mediated activation of monocytes by stimulated T lymphocytes is important for the production of TNFα and interleukin 1 in RA. Hyka et al demonstrated, in an experimental model, the ability of apolipoprotein A-I (apo A-I), the protein part of HDL cholesterol, to inhibit this inflammatory response.7 It appeared that apo A-I hampers the binding of T lymphocytes to monocytes with subsequent abolishing of TNFα and IL1 production. In addition to the contact mediated inhibition of monocytes, HDL cholesterol inhibits the expression of vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) in TNFα stimulated human cells.8

Altogether these data indicate an active modulating role of lipids in inflammation. It is important to realise that inflammation itself might alter the properties of HDL cholesterol. Atherosclerosis starts when low-density lipoprotein (LDL) cholesterol infiltrates the artery wall and is oxidised by reactive oxygen species to oxidised LDL cholesterol (ox-LDL cholesterol). Ox-LDL cholesterol leads to phospholipid release, activating endothelial cells, thereby initiating an inflammatory process that leads to the formation of foam cells and subsequent fatty streaks. Normal HDL cholesterol exerts its anti-atherogenic role by protecting LDL cholesterol from oxidation,9 in addition to the inhibition of the expression of adhesion molecules and its role in the reverse cholesterol transport. This anti-inflammatory HDL cholesterol can be distinguished from the so-called proinflammatory HDL cholesterol which does not have these properties and actually may promote inflammation.10 Recently, McMahon and colleagues showed that proinflammatory HDL cholesterol was detected more often in patients with RA (n=48) than in control subjects, (n=72) (ie, 20% vs 4%, respectively).11 This impairment of the ability of HDL cholesterol to prevent oxidation of LDL cholesterol might predispose RA to development of cardiovascular disease and effective antiinflammatory treatment might restore the functional capacities of HDL cholesterol.12

LIPID LOWERING AGENTS AND (THE DEVELOPMENT OF) RA

In view of the above-mentioned interplay between lipids and inflammation, it is of interest to study the effect of lipid modulation by cholesterol lowering agents, particularly statins, in inflammatory situations. It has been demonstrated that several statins significantly increase HDL cholesterol and apo A-I through upregulation of apo A-I synthesis, in vitro as well as in vivo.13 14 As a consequence, this could lead to modulation of inflammatory processes.

A pivotal feature of RA is inflammation associated bone destruction and as recent data indicate that statins are potent inducers of bone morphogenetic protein and osteoostrogenesis inhibitors,15 Funk et al investigated their potential bone protective properties.16 In an experimental rat arthritis model, simvastatin was given to female Lewis rats 4 days before or 8 days after induction of arthritis and simvastatin prevented early and late joint inflammation and this was associated with a decrease in articular macrophage influx. Moreover, simvastatin inhibited periarticular bone destruction occurring late in the course of disease and preserved periarticular bone mineral density. These results suggest that statins may be therapeutically useful in preserving periarticular bone in RA joints.

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via suppression of inflammation-induced bone resorption.

These properties of statins warranted further clinical investigation and after a small clinical investigation with simvas-
tatin revealed an impressive 50% reduc-
tion of disease activity in 9 out of 10 patients,7 a double-blind placebo-con-
trolled trial with another statin (atorvas-
tatin) in 116 patients with RA was con-
ducted.19 These patients were either treated with atorvastatin 40 mg or pla-
cebo for 6 months, in addition to their
disease-modifying antirheumatic drug
(DDMARD) therapy. At 6 months, there was a modest, but significant, improve-
ment of the disease activity (0.5 point on the
disease activity 28 score) in the
atorvastatin group compared to the pla-
cebo group with a CRP and erythrocyte
sedimentation rate decline of 50% and
28%, respectively. Obviously, there is now
a need for larger investigations with
longer follow-up, that investigate if, and
to what extent (and at what dose), statins
can prevent the bone destruction in RA.

Altogether, lipids and alteration of the
lipid profile by statins have the potential
to modulate inflammatory features of RA
and a tempting hypothesis is that they
therefore could also have a role in the
development of RA or other inflamma-
tory disorders. For instance, the West of
Scotland Coronary Prevention Study
(WOSCOPS) revealed 30% less new onset
diabetes in the men treated with pravas-
tatin vs the placebo-treated persons.19 One
of the explanations may be that pravas-
tatin lowers the levels of IL6 and TNFα
resulting in a decreased lipolysis in adi-
pose tissue and less insulin resistance, and
recently it was demonstrated that pravas-
tatin additionally increases the levels of
adiponectin, an adipose tissue derived
cytokine with anti-atherosclerotic and
insulin-sensitising functions.20

Likewise a lower incidence of RA would
also be expected in “normal” subjects
receiving lipid lowering drugs vs those
who did not, in controlled clinical trials
investigating these drugs. Unfortunately,
this topic has not yet been addressed in
such trials. However, a recent epidemi-
ologic investigation has shed some light
on this topic.21

The General Practice Research Database
was used in this nested case-control study
and this database was founded in 1987 and
presently encompasses 5 million UK
residents who are representative of the
UK population. The present study period
was 10 years (until 31 December 2001) and
three groups of subjects aged 40 to 89
years were identified from the database:
(a) patients exposed to a statin or other
lipid lowering drugs, (b) subjects with a
hyperlipidaemia diagnosis with no lipid-
lowering drugs and (c) a random sample of
25 000 persons with no hyperlipidaemia
or prescriptions for lipid-lowering drugs.

From the database population incident
cases of RA were identified and up to four
controls per case, matched on age, sex,
general practice, years of history in the
database and index date were selected.
Conditional logistic regression techniques
were used to investigate the effects of
hyperlipidaemia and statins on the devel-
opment of RA. A total of 313 incident
cases of RA were identified and matched
with 1252 controls. RA cases had hyperlip-
idaemia more often than controls, and
there was a 50% risk increase for RA in
those persons with untreated hyperlipi-
daemia (odds ratio (OR) 1.33, 95% CI 0.95
to 1.86) and persons with no hyperlipi-
daemia had a 50% risk decrease for RA
(OR 0.68, 95% CI 0.50 to 0.91).

Compared to persons with hyperlipi-
daemia but no statin, current statin use
reduced the risk for the development of
RA with 50% (those with statin and
hyperlipidaemia) to 40% (those with
statin without hyperlipidaemia, albeit
that this reduction did not reach statis-
tical significance). Subgroup analyses
revealed no important differences among
the three most commonly prescribed
statins (ie, simvastatin, pravastatin and
atorvastatin). Remarkably, lipid lowering
drugs other that statins were not asso-
ciated with a decreased risk. This might
be due to too low a patient number treated
with these drugs, a too limited effect on the
lipid profile or the absence of anti-
flammatory properties of these drugs.

This investigation reveals two impor-
tant points: (1) the association between
hyperlipidaemia and the development of
RA, which is in line with the findings of
van Halm et al8 and (2) that statins are
protective against development of RA in
those with hyperlipidaemia.

Future studies will have to address
whether or not statins really protect
against the development of RA or if they
only delay disease onset.

CONCLUSIONS

There is a growing body of evidence
indicating relationships between dyslipi-
daemia and (the development) of RA. At
least 10 years before disease onset there
is a disturbed lipid profile and future studies
should elucidate if this dyslipidaemia
renders a person more susceptible for the
development of RA, through proinflam-
matory mechanisms or if there is a
coupled genetic or socioeconomic back-
ground. As a consequence targeting dysli-
pidaemia may influence inflammation
and the development of inflammatory
disorders. Indeed, the literature suggests
that statins may have a moderate disease-
modifying effect in RA and this is, at least
partly, independent from their cholesterol
lowering properties and ascribed to their
pleiotropic anti-inflammatory actions.
Very recently, it appeared that these drugs
might also prevent (or retard) the devel-
opment of RA.

The challenge is obviously to translate the (presumed) RA preventing effect of
statins into clinical practice. Over the past
few years there has been a continuing
debate as to whether or not a polypill that
combines aspirin, a statin for lowering
cholesterol and an angioconverting
enzyme inhibitor with a thiazide to lower
blood pressure should be given to all
persons with an increased cardiovascular
risk (eg, elderly persons).22 23 Presently,
the first international placebo-controlled
trial has been initiated,24 which will be
followed by large-scale placebo-controlled
investigations when the first results
demonstrate that the polypill is tolerable
and efficacious. Perhaps, the combination
of all these trials might show a favourable
effect of statin/polypill on the incidence
of inflammatory diseases such as RA,
but that the number of incident cases
might still be too low.

The clinical use of statins is more
realistic in the context of cardiovascular
risk management in RA. When lipid
lowering therapy is necessary, statins are
preferred over other lipid lowering drugs,
as they not only target dyslipidaemia but
also have anti-inflammatory properties
and this is important as nowadays cardi-
vascular risk management in RA should
be targeted at the inflammatory process
as well as the cardiovascular risk factors.25

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