The course of clinically suspect arthralgia and early rheumatoid arthritis : clinical features, imaging and genetics

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Osteoprotegerin as biomarker for persistence of rheumatoid arthritis

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14

Sir, currently the treatment of Rheumatoid arthritis (RA) is aimed at achieving low disease activity score (DAS) remission. The ultimate aim, however, is to achieve disease-modifying antirheumatic drug (DMARD)-free sustained remission, which reflects the persistent absence of arthritis after cessation of treatment and is the closest proxy available for cure of RA. Although at present DMARD-free sustained remission can only be achieved in a minority of RA patients, recent data revealed that this outcome has become increasingly achievable due to improved treatment strategies [1]. The processes underlying resolution of disease persistence are unknown. An understanding of these processes might give clues for intervention targeted at disease resolutions. Furthermore, except for ACPA or RF, biomarkers for disease persistence are unknown. A recent study by Audo et al [2] prompted us to investigate the association between serum osteoprotegerin (OPG) levels and DAS remission as well as DMARD-free sustained remission. This study showed, using data of one cohort, that a low ratio of OPG to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) was associated with DAS28 remission (DAS <2.6) after 1 year and that this association was completely explained by the OPG level. OPG is a member of the tumor necrosis factor (TNF) superfamily molecules. Besides its well-known role in bone metabolism, OPG has pro-inflammatory effects that likely act via the nuclear factor (NF)-kB pathway. As such, OPG has been implicated as a disease activity marker for inflammatory bowel disease [3]. The present study has two aims: first, we sought for replication of the association of OPG levels with DAS remission, as replication of findings in independent cohorts is pivotal; and second, because OPG may associate with the severity of inflammation in the short-term, we explored the association of OPG levels with achieving DMARD-free sustained remission as long-term treatment outcome.

We studied 158 RA patients (1987 ACR criteria) included in the Leiden Early Arthritis Clinic cohort 4 between 1993 and 2005 (67% female, mean (SD) age 56.2 (13.5) years, 64% ACPA-positive). OPG levels were determined using ELISA [5,6] in sera collected at a median disease duration of 4 (range 1-9) years, while patients were treated with conventional DMARDs. At the moment of serum collection, the mean (SD) DAS44 was 2.3 (1.1), 53% of patients had a DAS44 <2.4 and none of the patients were in DMARD-free sustained remission. For analyses, OPG levels were stratified in quartiles with similar patient numbers. The outcomes were achieving DAS44 remission (DAS44 <2.4 and <1.6) 1 year after serum collection and; achieving DMARD-free sustained remission during follow-up (median follow-up 10 year, IQR 9-10 years). DMARD-free sustained remission was defined as the sustained absence of arthritis (by physical examination) after discontinuation of DMARD therapy, including biologics and glucocorticosteroids, for the entire follow-up and the follow-up should be at least one year after cessation of DMARD-treatment. Patients that relapsed during follow-up were not in the DMARD-free sustained remission group. All medical files were explored on this outcome until 5 April 2012 [1]. Logistic and Cox regression analyses were performed with adjustments for age, gender and treatment strategy [4]. The analyses of DAS44 remission were additionally adjusted for DAS44 at sample collection and the analysis of

DMARD-free sustained remission were additionally adjusted for disease duration at sample collection. All patients gave informed consent and approval was obtained from the medical ethics committee of the Leiden University Medical Center.

One hundred and sixteen patients (73.4%) and 67 patients (42.4%) had achieved DAS44 remission when, defined, respectively, as DAS <2.4 and DAS <1.6 1 year after serum collection. Per quartile decrease in OPG the odds ratio (OR) for achieving DAS44 remission during the next year was 1.65 (95% CI 1.11 to 2.47, p=0.014) when defining DAS44 remission as a DAS <2.4. Similar results were obtained when defining DAS44 remission as a DAS <1.6 during the next year (OR=1.55, 95% CI 1.084 to 2.22, p=0.016). Sixteen patients (10.1%) achieved DMARD-free sustained remission after a median of 6 years of disease (IQR 4-8) and 3 years (IQR 1-4) after serum collection. Lower OPG level associated significantly with a higher chance of DMARD-free sustained remission (hazard ratio on remission per quartile decrease in OPG level 1.92 (95% CI 1.043 to 3.52, p=0.036) (Figure 1).

In conclusion, we here replicated the finding that low OPG levels were predictive for an increased chance of DAS remission during the next year. The findings were similar when using DAS remission defined as DAS44 <2.4 or <1.6. These validated results suggest that OPG is a biomarker that might be useful to assess during treatment in order to predict the chance of a low disease activity during the next year. Interestingly, serum OPG levels were also associated with the chance of DMARD-free sustained remission. Together these data suggest that OPG levels are reflective of a process influencing the severity of inflammation both on the short and long-term. Intriguingly, OPG levels did not correlate with DAS remission at the same point in time. This may suggest that the change in OPG level precede the change in inflammation that is measured by the DAS. Longitudinal studies are needed to explore this. In addition further studies are needed to confirm the association between OPG levels and DMARD-free sustained remission and to investigate the mechanisms underlying this association. Because it is likely that achieving DMARD-free sustained remission will become a preferred treatment goal in the future, further studies are also required to examine whether serum OPG levels are useful to guide treatment decisions and to predict if this favourable disease outcome is achievable.

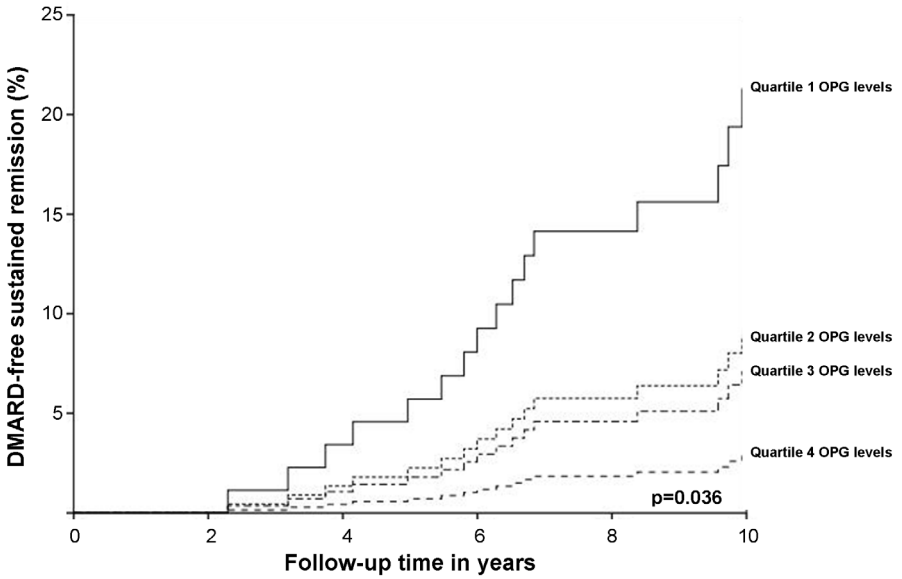

Figure 1. Osteoprotegerin levels in relation to achieving DMARD-free sustained remission in 158 rheumatoid arthritis patients. Depicted are the modeled (by the Cox regression analysis) percentages of 158 rheumatoid arthritis patients of the Leiden Early Arthritis Clinic cohort that achieved DMARD-free sustained remission during 10 years follow-up. Quartile 1 presents the lowest OPG levels and quartile 4 the highest level. The hazard ratio on achieving DMARD-free sustained remission was 1.92 (95% CI 1.043 to 3.52) per quartile decrease in OPG level (p=0.036). Quartile 1, 2, 3 and 4 concerned respectively 39, 40, 40 and 39 patients.

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