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Prognostic impact of Interleukin-1 receptor antagonist in patients with documented coronary artery disease

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ABSTRACT

Background: IL-1β-mediated inflammation contributes to development and progression of coronary artery disease (CAD). We aimed to assess the prognostic impact of the inflammatory marker Interleukin-1 receptor antagonist (IL1-Ra), reflecting high IL-1β activity, in patients with documented CAD.
Methods: IL-1Ra levels were determined in 1337 subjects of the Athero*Gene* study, a prospective cardiovascular registry comprising patients with CAD as detected by coronary angiography presenting with acute coronary syndrome (ACS) or stable angina. Median follow-up was 6.4 years.
Results: Patients with IL1-Ra levels in the highest tertile presented more often with ACS (55% vs. 40% vs. 34%, $p < 0.001$), were more commonly treated with PCI (47% vs. 39% vs. 34%, $p < 0.001$), had lower left ventricular ejection fraction (LVEF) (61 ± 15% vs. 62 ± 15% vs. 65 ± 14%, $p = 0.001$) and higher hs-CRP levels (10.0 vs. 4.2 vs. 2.5 mg/L, $p < 0.001$). IL1-Ra levels at baseline were predictive for all-cause mortality in the total study cohort after adjustment for conventional cardiovascular risk factors, LVEF, hs-CRP and Troponin T (adjusted HR 1.45 (95% CI 1.16–1.82), $p < 0.001$). In a subgroup of patients with ACS, but not in those with stable angina, IL1-Ra was an independent predictor for cardiovascular mortality (ACS: adjusted HR 1.85 (95% CI 1.33–2.58), $p < 0.001$; stable angina: adjusted HR: 1.25 (95% CI 0.95–1.65), $p = 0.11$).
Conclusion: IL1-Ra is an independent predictor for adverse outcome in patients with documented CAD, beyond the prognostic value of hs-CRP and Troponin T in particular in the setting of ACS. For CAD patients our finding might improve both, risk assessment in secondary prevention and patient selection for anti-inflammatory treatment.

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1. Introduction

Proinflammatory pathways contribute to the development and progression of coronary artery disease (CAD) [1,2]. Interleukin 1β (IL-1β) plays a key role in activating an inflammatory cascade, which modulates atherogenesis mediated by chemotactic and hemostatic properties of endothelial and smooth muscle cells in the vascular wall [3–6]. The IL-1 receptor antagonist (IL-1Ra) is an endogenous inhibitor of IL-1β [7]. IL-1Ra production is induced by IL-1β and, thus, is acting as a counter-regulator of IL-1β mediated processes [8–10]. In contrast to IL-1β, for which a direct measurement is not applicable due to extremely low plasma levels, the level of circulating IL-1Ra can be reliably quantified [11–13]. Therefore, IL-1Ra can serve as a detectable surrogate parameter for high IL-1β activity [14,15]. There is evidence that high levels of IL-1Ra are associated with incident cardiovascular disease in apparently healthy individuals [16–18]. However, only little is known about the prognostic impact of IL-1Ra in individuals with documented coronary artery disease in particular after acute coronary syndrome (ACS). Recently, this patient group was addressed to test the efficacy of IL-1 pathway inhibition [19]. The aim of the current study was to assess the association of IL-1Ra levels in a large cohort of patients with documented CAD.

2. Methods

2.1. Study population

The Athero*Gene* study has been described in detail previously [20]. Briefly, between 1996 and 2004 a total of 3312 patients presenting with ACS or stable angina and scheduled

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for coronary angiography were enrolled at two German centers. Acute myocardial infarction (MI) was either ST-segment elevation MI (STEMI) or non-ST-elevation MI (NSTEMI) based on clinical presentation and positive in-house troponin concentrations. Unstable angina was diagnosed according to the Braunwald classification [21]. The final diagnosis of ACS (STEMI, NSTEMI, or unstable angina) was made retrospectively based on the judgment of two physicians, with access to the history and nature of the presenting symptoms, medical history, results of physical examination, and of the medical records available from index hospitalization. CAD was diagnosed by coronary angiography with at least one stenosis >30% in a major coronary artery. Patients with significant comorbidities, e.g. cardiomyopathy, relevant valvular heart disease, malignant disease or febrile condition, were excluded from the study. Blood samples were collected from each patient at enrollment. Follow-up was obtained from either clinic visits or telephone interviews by trained medical staff and included information about all-cause mortality as well as cardiovascular death. The local ethics committee approved the study and each study subject gave written informed consent and participated voluntarily.

2.2. Laboratory methods

Blood samples were collected at fasting state before coronary angiography, immediately processed and stored at −80 °C until further analysis. Measurements of IL-1Ra levels were performed using an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA) which has been described elsewhere [17,22,23]. The assay provided a lower level of detection of 32.2 pg/mL and an intra- and inter-assay coefficient of variation of 3.59% and 5.68%, respectively.

2.3. Statistical analysis

Continuous variables were described as mean plus standard deviation or, in case of skew distributions, as quartiles; categorical variables as absolute numbers and percentages. All patients with available IL-1Ra measurement were included in the analysis and were split into three groups based on tertiles of IL-1Ra. Differences between these groups were investigated with *t*-tests or Mann–Whitney *U* tests (for continuous variables) or χ^2 tests (for categorical variables). Kaplan–Meier curves stratified by tertiles of IL-1Ra were generated and differences in survival among groups were tested using log-rank tests. To investigate associations between IL-1Ra and each of the end points a) death from any cause and b) cardiovascular death, multivariable Cox regression was used. The log of IL-1Ra was used as predictor of interest to account for the skewed distribution of IL-1Ra. Per end point, three models were built to account for confounding: model 1 was adjusted for age and sex; model 2 was additionally adjusted for conventional cardiovascular risk factors (BMI, arterial hypertension, smoking, diabetes, family history) and left ventricular ejection fraction (LVEF); model 3 additionally adjusted for log(hs-CRP); and model 4 (fully adjusted model) adjusted for log(troponin T) in addition to the variables of model 3. In subgroup analyses, Kaplan–Meier curves and Cox regression models were computed for ACS or stable angina patients only. Tertiles of IL-1Ra were computed for each subgroup separately.

3. Results

3.1. Baseline characteristics

A total of 1337 patients with available IL-1Ra measurement were included in the analysis. During a mean follow up time of 6.4 years 208 deaths of all-cause were documented, comprising 159 patients who died from cardiovascular causes. Baseline characteristics of the overall cohort and according to IL-1Ra tertiles are presented in Table 1. Patients were predominantly male and provided a broad spectrum of cardiovascular risk factors. The majority of patients presented with stable angina. Patients in the highest tertile of IL-1Ra, showed higher BMI, rate of smoking and diabetes and lower HDL cholesterol levels compared to patients in the lowest tertile. Moreover, in these patients higher levels of high-sensitivity hs-CRP and troponin I and T were detected. Patients in the highest tertile of IL-1Ra presented more often with ACS, were more commonly treated with PCI (either at index procedure or during follow-up), had lower LVEF and more often a history of myocardial infarction. There was no significant difference by means of SYNTAX score, presence of multivessel disease and total coronary artery occlusion according IL-1Ra tertile, yet, all of these variables were numerically higher in patients in the highest IL-1Ra tertile. The distribution of IL-1Ra among the total study cohort as well as in the subset of patients with stable angina and ACS is given in Supplementary Fig. Fig. 1. Baseline characteristics according to patients' clinical presentation, i.e. stable angina or ACS, are presented in Supplementary Table 1. In Supplementary Table 2 baseline characteristics of the study cohort and the total Athero*Gene* cohort are compared.

3.2. Outcome according to IL-1Ra level

Fig. 1A illustrates Kaplan–Meier curves for all-cause and cardiovascular mortality in the overall cohort stratified by IL-1-Ra tertile (T1 ≤ 211.6 pg/mL, T2 211.6–416.1 pg/mL, T3 > 416.1 pg/mL). Both, rate of all-cause mortality and cardiovascular death were higher in patients with higher IL-1-Ra levels. Fig. 1B depicts Kaplan–Meier curves for cardiovascular mortality in patients presenting with ACS ($N = 580$) and stable angina ($N = 757$). Among patients presenting with ACS, but not in those with stable angina, the rate of cardiovascular mortality was significantly higher in subjects with higher IL-1Ra levels. Overall, 11.4% of patients presenting with ACS and 12.3% of patients presenting with stable angina suffered from cardiovascular death during follow-up. The risk for a composite endpoint including cardiovascular mortality, non-fatal MI or stroke was higher for patients in the highest IL-1Ra tertile (hazard ratio T3 vs. T1: 1.33 (95% CI 1.17–1.52; $p < 0.001$)) among the total study cohort, as well as in the subgroups of patients with stable angina (hazard ratio T3 vs. T1: 1.32 (95% CI 1.10–1.58; $p = 0.0024$)) and ACS (hazard ratio T3 vs. T1: 1.38 (95% CI 1.14–1.68; $p = 0.0011$)).

3.3. Prognostic impact of IL-1Ra after multiple adjustment

The impact of IL-1Ra on all-cause mortality is shown in Fig. 2. Higher levels of IL-1Ra were associated with increased all-cause mortality across all models of adjustment, with a hazard ratio (HR) of 1.45 (95% CI 1.16–1.82), $p < 0.001$ after full adjustment. Fig. 3 displays the impact of IL-1Ra on cardiovascular mortality after full adjustment for the total patient cohort as well as for the ACS and stable angina subgroups. Higher IL-1Ra levels were associated with a higher risk for cardiovascular death among all patients. The strongest impact on cardiovascular mortality was observed in patients presenting with ACS with a HR of 1.85 (95% CI 1.33–2.58), $p < 0.001$. In contrast, in patients presenting with stable angina the IL-1Ra level showed no significant impact on cardiovascular mortality after full adjustment. Hazard ratios for all-cause mortality for patients with ACS and stable angina are provided in Supplementary Table 3.

4. Discussion

The present study assessed the association of IL-1Ra levels and mortality in patients with documented CAD presenting with either ACS or stable angina. We found that CAD patients with higher IL-1Ra levels presented more often with ACS, had poorer left ventricular function, were more often in need for PCI and had higher levels of inflammation. Most importantly, in such patients IL-1Ra levels independently predicted all-cause and cardiovascular mortality and had the strongest impact on adverse outcome in those presenting with ACS.

4.1. IL-1Ra and its association with cardiovascular disease

The association of circulating IL-1Ra levels and cardiovascular disease has previously been investigated in population-based [17,18] and prospective cohort studies comprising patients with type 2 diabetes [24]. These studies found a positive association of IL-1Ra levels and the incidence of cardiovascular disease independent of conventional risk factors. In patients with a history of cardiovascular disease IL-1Ra levels were an independent predictor for major adverse cardiovascular events [25]. Our study corroborates these findings, as we demonstrate in patients with evident CAD that subjects with higher IL-1Ra levels presented more often with ACS and reduced left ventricular function and had a poorer prognosis. Thus, our data underline the importance of the IL-1 pathway in the development and progression of cardiovascular disease and are in line with the results shown in the CANTOS trial. Here, in patients with a history of myocardial infarction and at a state

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