Change over time of lipid profile relates to steroid treatment but not to an inflammatory state in Granulomatosis with poliangioitis polyangiitis (GPA)

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Aim: Granulomatosis with polyangiitis (GPA) is a small vessel vasculitis. Inflammation of the vessel wall may induce multiple vascular damages. Atherosclerosis is accelerated during vasa inflammation. Metabolic profile and cardiovascular risk are far to be determined in these patients. Thus, Cardiovascular atherosclerotic disease (ASCVD) may represent a risk for patients' outcomes. The purpose is to evaluate ASCVD risk in GPA over time during disease follow-up.
Methods: We retrospectively evaluated 37 patients (22 Females, aged 51.45±17.15) who received a diagnosis of GPA (T0). Patients were evaluated at 1 (T1) and 2 (T2) year follow-up. All patients were treated with high steroid dose followed by a one-year tapering, associated to another immunosuppressant. Lipid profile included total cholesterol, HDL, LDL and Triacylglycerol. To evaluate inflammatory activity, we evaluate erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and neutrophil to lymphocyte ratio (NLR) at the same time points. ANOVA for repeated values was used to evaluate the trend over time and Tukey's multiple comparisons test was a second step evaluation.
Results: At T1 there was an increase in total cholesterol compared to baseline (T1vsT0, $p<0.05$) and T2 (T1vs T2, $p<0.05$). Similarly, LDL (T1vsT0, $p<0.05$) presents the same trend, while Triacylglycerol increased in T1 compared to baseline (T1vsT0, $p<0.05$), but no difference there was in T2 compared to T1 or T0. No difference was found in HDL between the different time points. CRP was no different, despite a reduction being noticed. On the contrary, we found a reduction at T2 but not in T1 in ESR (T1vsT0, $p<0.05$) and NLR (T1vsT0, $p<0.05$).
Conclusion: Our data suggest that a change in lipid profile may not relate to better control of inflammation. On the contrary, the increase in the first year of follow-up should be a consequence of steroid treatment needed to spread disease control. These data may be helpful in the evaluation of both cardiovascular disease and lipid metabolism due to the connection between the two parameters with vessel inflammation. Further studies are needed to better evaluate the cardiovascular effect of vasculitis and consequent treatment.

Impact of immune system humanization on atherosclerosis in dyslipidemic Rag2-KO/IL2rg-KO/CD47-KO/ LDL-R KO mice

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Aim: Given the key role of the immune response during atherosclerosis and the therapeutic interest of biologics targeting human immune cells, the need of experimental models to translate molecular mechanisms and to test therapeutic approaches for atherosclerosis is continuously increasing. Here we describe the characteristics of an innovative immunodeficient mouse humanized with hCD34+ cells on an atheroprone background.
Methods: LDLR-KO mice were crossed with the immunodeficient C57BL/6J strain Rag2-KO/IL2rg-KO/CD47-KO (TKO, IMSR_JAX: 025730) to generate an immunocompromised dyslipidemic mouse TKO-LDLR KO recipient of human hematopoietic stem cells (hCD34+).
Results: TKO-LDLR KO were first characterized for their immune and metabolic profile. TKO mice are deficient in mature lymphocytes and NK cells and this profile was conserved in TKO-LDLR KO mice. Under high cholesterol diet for 8 weeks, both males and females TKO-LDLR KO present monocytosis with increased levels of Ly6Chi monocytes compared to TKO-LDLR KO at standard diet, develop marked dyslipidemia (total cholesterol 870.9 and 890.1 mg/dL male and females respectively), steatosis and atherosclerosis. This profile confirms the suitability of TKO-LDLR KO mice for atherosclerosis studies. Next, we tested the impact of immune system humanization. TKO-LDLR KO pups received a low-dose irradiation (150-200 cGy) and thereafter 1,5-2 x 10^5 hCD34+ were injected with in the liver. Engraftment of human leukocytes (hCD45+) was evaluated after two months by flow cytometry analysis from tail blood. This approach allows to reconstitute between 10-30% of hCD45+, mainly B and T cells.
Conclusions: We have generated and characterized for the first time a humanized dyslipidemic TKO-LDLR KO mouse. This mouse model presents human B and T cells and could represent an important tool to investigate the impact of biologics targeted toward human targets in the context of atherosclerosis.