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Serum level of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) is a biomarker of synovitis in rheumatoid arthritis

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Triggering Receptor Expressed on Myeloid cells-1 (TREM-1) is a receptor mainly expressed on monocytes and neutrophils, involved in the amplification of the immune response during both bacteria and sterile inflammation [1]. Following engagement, TREM-1 is shed and may be detected in the blood. In patients admitted for myocardial infarction, plasma levels of soluble TREM-1 (sTREM-1) has been identified as an independent predictor of ischemia recurrence and death.[2] In rheumatoid arthritis (RA), TREM-1 is over-expressed in synovial tissues and its pharmacological inhibition limits destructive lesions of collagen-induced arthritis [3,4]. Few works suggested that serum sTREM-1 level may reflect RA disease activity, but they included small sample size of patients and the association between serum sTREM-1 level and subsequent treatment response has never been addressed [5,6]. Therefore, we aimed to investigate whether sTREM-1 serum level is associated with disease activity and/or can predict response to biologic agent in RA patients. This is an ancillary study of the Rotation or Change trial (NCT NCT01000441) in which 300 RA patients with an inadequate response to a 1st line anti- TNFα agent were randomized to switch to either a 2nd anti- TNFα or a non-anti- TNFα agent [7].

Baseline serum sTREM-1 level was assessed in 272 patients with available serum samples using enzyme-linked immunosorbent assay (ELISA) (Quantikine, R&D Systems, Lille, France). The characteristics of the patients are reported in the **Table 1**. Among the patients assigned to the second anti-TNFα group, 106/133 patients (79.7%) received a concomitant synthetic DMARD and 68/133 (51.1%) received concomitant oral corticosteroids with a mean (SD) dose of 7.3 (3.0)mg/d. Among the patients assigned to the non-anti-TNFα group 102/139 (73.4%) received a concomitant synthetic DMARD and 77/139 (55.4%) received concomitant oral corticosteroids with a mean dose of 7.4 (2.9)mg/d, all $p > 0.05$. Good or moderate EULAR response at week 24 (W24) was achieved in 51.9% patients in the 2nd anti- TNFα group vs 66.9% patients in the non-anti- TNFα group ($p=0.01$).

Serum sTREM-1 level was detectable in all patients (mean level (standard deviation) 471.1 (242.0) pg/mL). sTREM-1 level was higher in men when compared to women (585.0 (240.1) pg/mL versus 447.9 (236.3) pg/mL, $p=0.0004$), but was not associated with seropositivity status nor correlated with body mass index. Serum sTREM-1 levels was higher in patients with DAS28-CRP>5.1 (542.5 (279.6) pg/mL) than in those with DAS28-CRP$\leq$5.1 (433.3 (212.5) pg/mL; $p<0.01$) (non-parametric Wilcoxon test). Such a result persisted after adjusting for sex ($p=0.005$). Using Spearman coefficients, we found that sTREM-1 level was positively correlated with DAS28-CRP value ($r=0.25$, $p<0.001$) (**Figure 1A**), due to its correlation with CRP level ($r=0.38$, $p<0.0001$), but also to specific assessments of RA (patient global

assessment r=0.14 and swollen joint count r=0.20, $p < 0.05$) (**Figure 1B**). sTREM-1 level was still significantly associated with swollen joint count after adjustment on CRP level in a regression analysis model (β=0.017, p=0.008).

Concerning the association with clinical response at W24, mean baseline sTREM-1 levels did not differ between W24 good and moderate EULAR responders versus non-responders in the whole population (459.9 (217.0) versus 487.6 (275.0) pg/mL, p>0.05). Similar results were obtained in the 2nd anti- TNFα group (450.8 (210.2) versus 502.7 (291.6) pg/mL, p>0.05) as well as in the non-anti- TNFα group (466.7 (22.7) versus 466.6 (251.7) pg/mL, p>0.05).

In conclusion, serum sTREM-1 level may be a new interesting marker for RA disease activity. Serum sTREM-1 level does not only reflect systemic inflammation (*i.e.*, CRP level) but also clinical joint inflammation, suggesting a specific role of this myeloid receptor in rheumatoid synovitis pathophysiology. Along this line, longitudinal assessment of serum sTREM-1 before and after treatment would be interesting

References:

1. Tammaro A, Derive M, Gibot S, Leemans JC, Florquin S, Dessing MC. TREM-1 and its potential ligands in non-infectious diseases: from biology to clinical perspectives. Pharmacology & Therapeutics. sept 2017;177:81-95.

2. Boufenzer A, Lemarie J, Simon T, Derive M, Bouazza Y, Tran N, et al. TREM-1 Mediates Inflammatory Injury and Cardiac Remodeling Following Myocardial Infarction. Circulation Research. 22 mai 2015;116(11):1772-82.

3. Kuai J, Gregory B, Hill A, Pittman DD, Feldman JL, Brown T, et al. TREM-1 expression is increased in the synovium of rheumatoid arthritis patients and induces the expression of pro-inflammatory cytokines. Rheumatology. 1 nov 2009;48(11):1352-8.

4. Murakami Y, Akahoshi T, Aoki N, Toyomoto M, Miyasaka N, Kohsaka H. Intervention of an inflammation amplifier, triggering receptor expressed on myeloid cells 1, for treatment of autoimmune arthritis. Arthritis & Rheumatism. juin 2009;60(6):1615-23.

5. Molad Y, Ofer-Shiber S, Pokroy-Shapira E, Oren S, Shay-Aharoni H, Babai I. Soluble triggering receptor expressed on myeloid cells-1 is a biomarker of anti-CCP-positive, early rheumatoid arthritis. European Journal of Clinical Investigation. juin 2015;45(6):557-64.

6. Choi ST, Kang E-J, Ha YJ, Song J-S. Levels of Plasma-soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1) Are Correlated with Disease Activity in Rheumatoid Arthritis. The Journal of Rheumatology. 1 mai 2012;39(5):933-8.

7. Gottenberg J-E, Brocq O, Perdriger A, Lassoued S, Berthelot J-M, Wendling D, et al. Non–TNF-Targeted Biologic vs a Second Anti-TNF Drug to Treat Rheumatoid Arthritis in Patients With Insufficient Response to a First Anti-TNF Drug: A Randomized Clinical Trial. JAMA. 20 sept 2016;316(11):1172-80.

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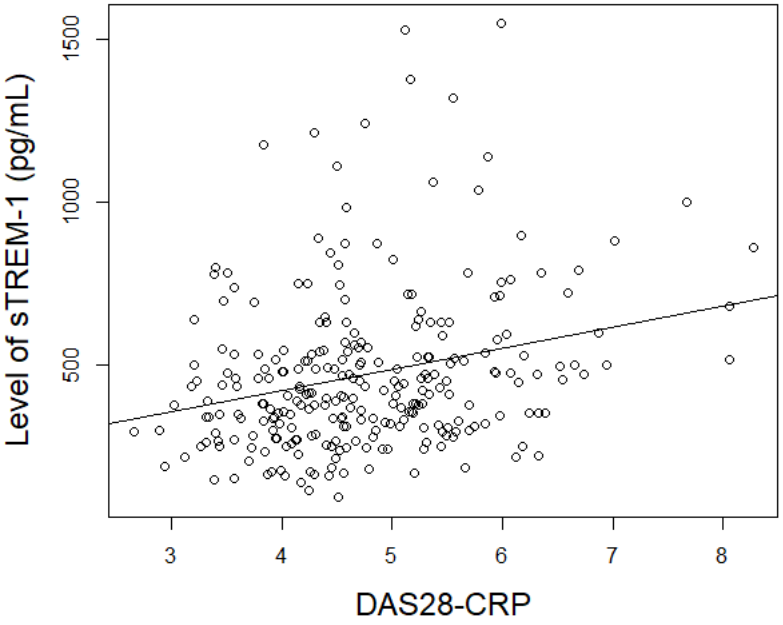
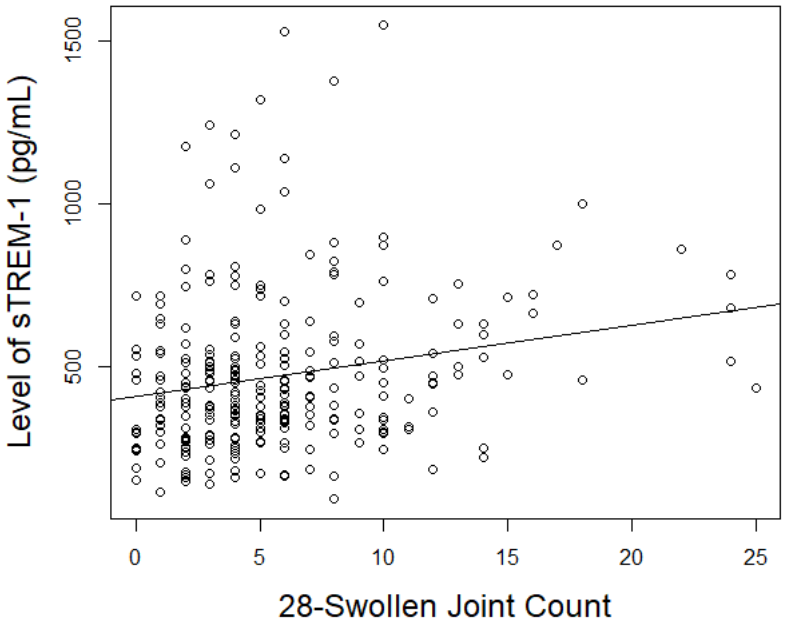
Conflict of interest: none

Figure 1. Correlation of serum sTREM-1 levels with disease activity features in 272 patients with rheumatoid arthritis and insufficient response to a first anti-TNF therapy

1A. Correlation between serum sTREM-1 levels and DAS28-CRP values



1B. Correlation between serum sTREM-1 levels and 28-Swollen Joint Count



sTREM-1: soluble Triggering Receptor Expressed on Myeloid cells-1; DAS28-CRP: Disease Activity Score 28-C reactive protein; TNF : Tumor Necrosis Factor.

sTREM-1 level was positively correlated with DAS28-CRP value (r=0.25, p<0.001) (**1A**) and also to specific assessments of rheumatoid arthritis as swollen joint count (r=0.20, p < 0.05) (**1B**).