EJR European Journal of Rheumatology

DOI:10.5152/eurjrheum.2023.22051

Letter to the Editor

Anti-Triggering Receptor Expressed on Myeloid Cells-Like Transcript-1 Antibodies in Systemic Lupus Erythematosus

Luis M. Vilá[1], Mariely Nieves-Plaza[2], Xariana Vales Torres[3], Benjamín Nieves[3], A. Valance Washington[3,4]

To the Editor

The Triggering Receptor Expressed on Myeloid Cells-Like Transcript-1 (TLT-1) is a platelet receptor that appears to have a role in inflammation and thrombosis.[1] Previously, we reported that patients with systemic lupus erythematosus (SLE) had significantly lower levels of soluble TLT-1 (sTLT-1) when compared to healthy individuals.[2] Thus, we thought to determine if lower sTLT-1 levels are associated with the presence of anti-TLT-1 antibodies in SLE patients and if anti-TLT-1 antibodies are linked with SLE clinical features.

Anti-TLT-1 antibodies were measured by enzyme-linked immunosorbent assay (ELISA) from stored plasma samples of the same SLE patients and healthy individuals that we previously reported and using sTLT-1 developed in-house.[1,2] The ELISA was developed according to Pierangeli and Harris.[3] Among SLE patients, we examined associations of anti-TLT-1 antibodies with demographic factors, SLE manifestations (per 1997 American College of Rheumatology (ACR) modified classification criteria), pharmacologic profile, comorbidities, disease activity (per the revised SLE activity measure (SLAM-R)), and the disease damage (per Systemic Lupus International Collaborating Clinics Damage Index). Student's *t*-test, Mann–Whitney *U* test, Pearson correlation coefficient, or Spearman's rank order correlation were used, as appropriate, for statistical analysis.

Forty-six SLE patients and 28 healthy subjects were studied. Healthy individuals had no comorbidities and were not taking any medication. No differences were observed for anti-TLT-1 antibodies between SLE patients and healthy individuals (1.05 ± 1.24 vs. 0.83 ± 0.81 μg/mL, $P = .83$) (Table 1). Among SLE patients, no correlation was found between anti-TLT1 antibodies and sTLT-1 levels ($r = 0.034$, $P = .776$). On the other hand, anti-TLT-1 antibody levels were significantly lower in 2 patients who had arterial thrombosis (0.00 ± 0.00 vs. 1.09 ± 1.25 μg/mL, $P = .022$) and in 3 patients who had venous thrombosis (0.03 ± 0.06 vs. 1.12 ± 1.26 μg/mL, $P = .044$) when compared to those who had no thrombotic events (Figure 1). Also, a negative correction was found for the SLAM-R score ($r = -0.291$, $P = .049$). No associations were found for age, gender, ACR SLE criteria, anti-phospholipid antibodies, comorbidities (diabetes mellitus, hypertension, overweight/obesity, and dyslipidemia), exposure to corticosteroids or immunosuppressive agents, or damage accrual.

The negative association that we found of anti-TLT-1 antibodies with arterial and venous thrombotic events was not unexpected. TLT-1 regulates early clot formation through the stabilization of αIIbβ3 which is a heterodimeric multidomain structure that mediates platelet aggregation through its interaction with fibrinogen.[1] Thus, antibodies against TLT-1 may have an antithrombotic effect. In fact, *in vitro* studies have shown that anti-TLT-1 antibodies inhibit thrombin-mediated platelet aggregation in humans.[4] Likewise, the negative correlation of anti-TLT-1 antibodies was not surprising. TLT-1 promotes

Table 1. Demographic Characteristics, TLT-1 Levels, and Anti-TLT-1 Antibodies in Healthy Controls and SLE Patients

Feature	SLE Patients (n = 46)	Healthy Individuals (n = 28)	*P*
Age, mean years (SD)	45.5 (11.8)	37.3 (12.1)	.081
Sex, % female	93.5	92.9	>.999
TLT-1 levels, mean pg/mL (SD)	9.0 (7.2)	18.6 (22.3)	.008
Anti-TLT-1 antibodies, μg/mL (SD)	1.05 (1.24)	0.83 (0.81)	.830

SLE, systemic lupus erythematosus; TLT-1, triggering receptor expressed on myeloid cells-like transcript-1.

ORCID iDs of the authors:
L.M.V.: 0000-0002-6679-2704;
M.N.-P.: 0000-0002-8105-5411;
X.V.T.: 0000-0002-8541-6771;
B.N.: 0000-0001-9184-1398;
A.W.: 0000-0002-3458-1822.

Cite this article as: Vilá LM, Nieves-Plaza M, Vales Torres X, Nieves B, Valance Washington A. Anti-triggering receptor expressed on myeloid cells-like transcript-1 antibodies in systemic lupus erythematosus. *Eur J Rheumatol* 2023;10(2):88-89.

[1] Division of Rheumatology, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico
[2] Universidad Central del Caribe School of Medicine, Bayamón, Puerto Rico
[3] Department of Biology, University of Puerto Rico, Río Piedras Campus, San Juan, Puerto Rico
[4] Department of Biological Sciences, Oakland University, Rochester, Michigan, USA

Corresponding author:
Luis M. Vilá
E-mail: luis.vila2@upr.edu

Received: April 11, 2022
Accepted: March 02, 2023
Publication Date: May 25, 2023

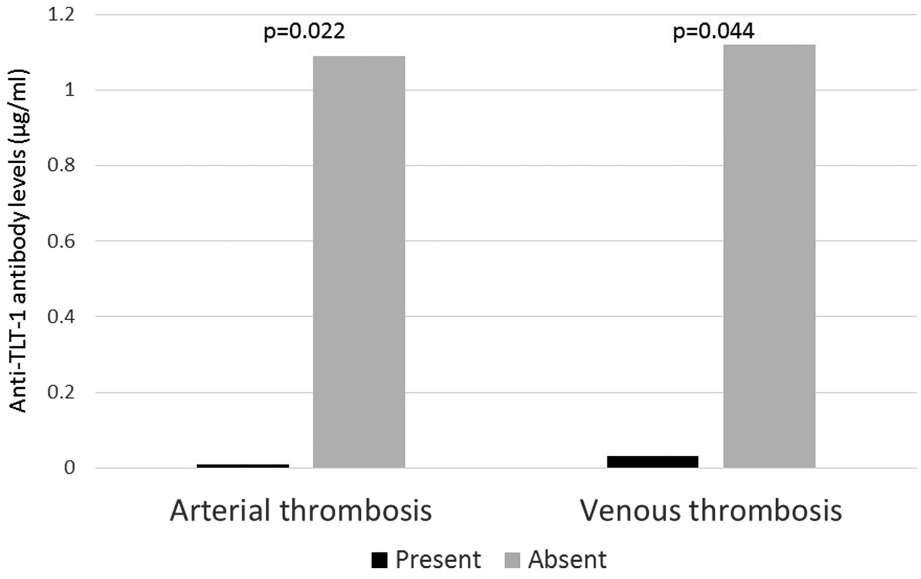

Figure 1. Anti-TLT-1 antibody levels in SLE patients with and without arterial and venous thrombosis. SLE, systemic lupus erythematosus; TLT-1, triggering receptor expressed on myeloid cells-like transcript-1.

platelet-monocyte aggregates enhancing interleukin (IL)-1β and IL-6 production from monocytes; therefore, blocking the effect of TLT-1 could have an anti-inflammatory effect.[5] Taken together, anti-TLT-1 antibodies may have a protective role in SLE by regulating the immune and coagulation homeostasis.

The main limitation of this work was the small sample size. The low statistical power undermined the likelihood of detecting significant differences. Also, we could not present categorical data of anti-TLT-1 antibody levels in terms of positive or negative results as a larger number of controls and individuals with SLE would be required to statistically calculate the cut-off value. Therefore, larger and longitudinal studies are required to further elucidate the role of anti-TLT-1 antibodies in the pathogenesis of SLE.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of the University of Puerto Rico Medical Sciences Campus (Approval No: 64103).

Informed Consent: Written informed consent was obtained from each participant who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – L.M.V, A.V.W; Design – L.M.V., M.N.P., A.V.W.; Supervision – L.M.V, A.V.W.; Funding – A.V.W; Materials – X.V.T., B.N., A.V.W.; Data Collection and/or Processing – L.M.V., X.V.T., B.N., A.V.W.; Analysis and/or Interpretation – L.M.V., M.N.P., A.V.W; Literature Review – L.M.V., A.V.W.; Writing – L.M.V., M.N.P., A.V.W; Critical Review – L.M.V, M.N.P., X.V.T., B.N., A.V.W.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: Research reported in this publication was supported by the NIH grants (R01HL090933 and HL140628), from the National Heart Lung and Blood Institute, and grant (5R25GM061151-20) from the National Institute of General Medical Sciences.

References

1. Branfield S, Washington AV. The enigmatic nature of the triggering receptor expressed in myeloid cells-1 (TLT-1). *Platelets*. 2021;32(6):753-760. [CrossRef]
2. Vázquez-Otero I, Rodríguez-Navedo Y, Vilá-Rivera K, et al. Association of soluble TREM-like transcript-1 with clinical features and patient reported outcomes in systemic lupus erythematosus. *Eur J Rheumatol*. 2018;5(4):244-248. [CrossRef]
3. Pierangeli SS, Harris EN. A protocol for determination of anticardiolipin antibodies by ELISA. *Nat Protoc*. 2008;3(5):840-848. [CrossRef]
4. Giomarelli B, Washington VA, Chisholm MM, et al. Inhibition of thrombin-induced platelet aggregation using human single-chain Fv antibodies specific for TREM-like transcript-1. *Thromb Haemost*. 2007;97(6):955-963. [CrossRef]
5. Wang M, Li X, Wang Q, et al. TLT-1 promotes platelet-monocyte aggregate formation to induce IL-10-producing B cells in tuberculosis. *J Immunol*. 2022;208(7):1642-1651. [CrossRef]