

Differential serum levels of interleukin-37 in patients with tumour necrosis factor receptor-associated periodic syndrome (TRAPS)

Sirs,

Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory disease caused by mutations in the *TNFRSF1A* gene. It is mostly characterised by recurrent fever episodes, abdominal pain, migratory skin rash, lymphadenopathy, myalgia, conjunctivitis, periorbital oedema, and serositis (1). TRAPS mutations are distinguished into low-penetrance (LP) variants (as p.R92Q and p.P46L), generally associated with delayed disease onset or milder phenotype, and high-penetrance (HP) variants (as p.C30R, p.C33Y, p.C43G, p.C52Y, p.C55Y and p.T50M), more frequently related to a severe phenotype, an early disease onset, higher number of fever episodes per year, and higher risk of developing AA amyloidosis (2, 3).

Interleukin (IL)-37 is an anti-inflammatory cytokine belonging to the IL-1 family and capable to counteract inflammation-mediated tissue damage by binding to the specific IL-18R1/IL-1Rrp receptor (4). Accumulating evidences show that IL-37 are altered in several chronic inflammatory diseases, including adult-onset Still's disease, Behçet's disease and rheumatoid arthritis (5-8). Therefore, we assessed the circulating levels of IL-37 in patients with TRAPS and looked for any association or correlation with clinical, laboratory and genetic features. To this end, a written informed consent was obtained from all patients and the study protocol was reviewed and approved by the University of Siena Institutional Ethics Committee.

We retrospectively collected 81 serum samples from 31 TRAPS patients (16 males, 15 females) carrying both HP-mutations (19 patients, 37 serum samples), including p.C43R 5/37; p.C43Y 1/37; p.T50M 12/37; p.C52Y 7/37; p.C55Y 1/37; p.S59N 1/37; p.S59P 1/37; p.C88Y 3/37; p.C88G/p.R92Q 2/37; p.C96R 1/37; Del 103-104 1/37; p.C114W 1/37 and L167-175del 1/37, and LP-mutations (12 patients, 44 serum samples), including p.R92Q 18/44; p.D12E 8/44; p.P46L 2/44; p.R104Q 4/44 and p.V95M 12/44. In 29/81 cases (anakinra, n=17; canakinumab, n=12) serum samples were obtained from patients treated with anti-IL-1 therapies. Table I summarises the patients' demographic and clinical information.

IL-37 serum levels were significantly increased in HP-TRAPS patients compared with LP-ones ($p=0.002$). Moreover, IL-37 serum levels were significantly lower among patients receiving anti-IL-1 therapy

Table I. Demographic, laboratory and clinical characteristics of TRAPS patients with low-penetrance *TNFRSF1A* variants (LP-TRAPS) and high-penetrance *TNFRSF1A* variants (HP-TRAPS).

| | LP-TRAPS (n=12) | | | HP-TRAPS (n=19) | | | p-value |
|-----------------------------------|-----------------|-------|-------|-----------------|-------|-------|---------|
| | Mean | SD | % | Mean | SD | % | |
| Females, % | | | 50.00 | | | 47.37 | 0.886 |
| Age | 40.33 | 11.67 | | 40.05 | 11.21 | | 0.974 |
| Disease onset (years) | 33.42 | 17.23 | | 12.21 | 14.94 | | 0.004 |
| Duration of disease (years) | 6.917 | 7.868 | | 27.84 | 15.65 | | < 0.001 |
| Duration of attacks (>7 days), % | | | 36.36 | | | 78.95 | 0.046 |
| Chronic course, % | | | 18.18 | | | 63.16 | 0.026 |
| SAA range mg/L (mean±SD) | 647.1 | 761.9 | | 307 | 533.2 | | 0.171 |
| SAA >20 mg/L | | | 75.00 | | | 57.89 | 0.45 |
| Amyloidosis, % | | | 0.00 | | | 27.78 | 0.066 |
| Thoracic pain, % | | | 33.33 | | | 16.67 | 0.61 |
| Pharyngitis, % | | | 27.27 | | | 0.00 | 0.27 |
| Aphthosis, % | | | 33.33 | | | 0.00 | 0.25 |
| Skin, % | | | 25.00 | | | 50.00 | 0.34 |
| Lymphadenopathy, % | | | 16.67 | | | 33.33 | 0.57 |
| Pericarditis, % | | | 41.67 | | | 0.00 | 0.11 |
| Pleurisy, % | | | 8.33 | | | 0.00 | 1.00 |
| Abdominal pain, % | | | 8.33 | | | 33.33 | 0.25 |
| Myalgia, % | | | 50.00 | | | 50.00 | 1.00 |
| Arthralgia, % | | | 50.00 | | | 33.33 | 0.64 |
| Arthritis, % | | | 8.33 | | | 50.00 | 0.08 |
| Conjunctivitis, % | | | 16.67 | | | 16.67 | 1.00 |
| Periorbital oedema, % | | | 8.33 | | | 0.00 | 1.00 |
| Disease activity, % | | | 66.67 | | | 68.42 | 1.00 |
| Patients on biologic treatment, % | | | 8.33 | | | 10.53 | 1.00 |

HP: high penetrance; LP: low penetrance; SAA: serum amyloid-A.

than in those who did not undergo IL-1 inhibition ($p<0.001$). Subdividing patients into subgroups, no statistical differences were observed between patients with inactive and active disease ($p=0.103$) as well as between those showing increased serum amyloid A (SAA) levels (>20 mg/L) and normal SAA levels (≤ 20 mg/L) ($p=0.833$). An inverse correlation was identified between IL-37 levels and age at disease onset ($r=-0.396$, $p<0.01$), while a positive correlation was found between IL-37 serum levels and disease duration ($r=0.339$, $p=0.002$), number of attacks per year ($r=0.285$, $p=0.01$) and global duration of attacks ($r=0.331$, $p=0.003$). Conversely, no significant correlations were observed between IL-37 serum levels and C-reactive protein ($p=0.280$), erythrodeposition rate ($p=0.227$) and SAA ($p=0.091$).

No differences were found in serum IL-37 levels in the subgroup of HP-TRAPS patients regarding disease activity and treatment ($p=0.672$ and $p=0.370$, respectively). Conversely, LP-TRAPS patients displayed decreased IL-37 levels after starting anti-IL-1 treatment ($p<0.001$).

According with recent studies, proinflammatory stimuli such as lipopolysaccharide (LPS) and various cytokines including IL-1 β , IL-18, and TNF- α , induce a prompt increase of IL-37 levels, which have been found deregulated in different autoinflammatory and autoimmune diseases (4-8). Actually, IL-37 acts as a negative feedback inhibitor in inflammatory contexts exerting its anti-inflammatory effects in several models (4, 9). These evidences could even partly explain our results as a biological at-

tempt to counteract TRAPS inflammation. In this perspective, our data further support the effective role of IL-1 blockade in controlling TRAPS-related inflammation (10). In conclusion, the results obtained in TRAPS patients are in agreement with previous studies supporting the biologic role of increased serum IL-37 levels in counteracting inflammation. Future studies should investigate whether IL-37 serum levels represent a possible biomarker of subclinical TRAPS activity.

O.M. LUCHERINI¹, PhD
 A. VITALE¹, MD
 L. OBICI¹, MD
 J. SOTA¹, MD
 B. FREDIANI¹, MD
 G. MERLINI², MD
 D. RIGANTE^{3,4}, MD, PhD
 L. CANTARINI¹, MD, PhD

¹Research Centre of Systemic Autoinflammatory Diseases, Behçet's Disease Clinic and Rheumatology-Ophthalmology Collaborative Uveitis Centre, Department of Medical Sciences, Surgery and Neurosciences, University of Siena; ²Amyloidosis Research and Treatment Centre, Fondazione IRCCS Policlinico San Matteo, Pavia;

³Institute of Paediatrics, Università Cattolica Sacro Cuore, Rome; ⁴Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.

Please address correspondence to:

Dr Luca Cantarini, Research Centre of Systemic Autoinflammatory Diseases, Behçet's Disease and Rheumatology-Ophthalmology Collaborative Uveitis Centre, Department of Medical Sciences, Surgery and Neurosciences, Policlinico "Le Scotte", University of Siena, viale Bracci 1, 53100 Siena, Italy.
 E-mail: cantariniluca@hotmail.com

Letters to the Editors

and to Dr Orso Maria Lucherini,
Research Centre of Systemic Autoinflammatory
Diseases, Behçet's Disease and Rheumatology-
Ophthalmology Collaborative Uveitis Centre,
Department of Medical Sciences, Surgery
and Neurosciences, Policlinico "Le Scotte",
University of Siena, viale Bracci 1,
53100 Siena, Italy.

E-mail: lucheriniom@gmail.com

Competing interests: none declared.

© Copyright CLINICAL AND
EXPERIMENTAL RHEUMATOLOGY 2019.

References

1. MCDERMOTT MF, AKSENTIJEVICH I, GALON J *et al.*: Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell* 1999; 97: 133-44.
2. AGANNA E, HAMMOND L, HAWKINS PN *et al.*: Heterogeneity among patients with tumor necrosis factor receptor-associated periodic syndrome phenotypes. *Arthritis Rheum* 2003; 48: 2632-44.
3. LACHMANN HJ, PAPA R, GERHOLD K *et al.*: The phenotype of TNF receptor-associated auto-inflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EURO-TRAPS international registry. *Ann Rheum Dis* 2014; 73: 2160-7.
4. CAVALLI G, DINARELLO CA: Suppression of inflammation and acquired immunity by IL-37. *Immunol Rev* 2018; 281: 179-90.
5. CHI H, LIU D, SUN Y *et al.*: Interleukin-37 is increased in adult-onset Still's disease and associated with disease activity. *Arthritis Res Ther* 2018; 20: 54.
6. NOLD MF, NOLD-PETRY CA, ZEPP JA, PALMER BE, BUFLER P, DINARELLO CA: IL-37 is a fundamental inhibitor of innate immunity. *Nat Immunol* 2010; 11: 1014-22.
7. ZHAO PW, JIANG WG, WANG L, JIANG ZY, SHAN YX, JIANG YF: Plasma levels of IL-37 and correlation with TNF- α , IL-17A, and disease activity during DMARD treatment of rheumatoid arthritis. *PLoS One* 2014; 9: e95346.
8. BOUALI E, KAABACHI W, HAMZAOUI A, HAMZAOUI K: Interleukin-37 expression is decreased in Behçet's disease and is associated with inflammation. *Immunol Lett* 2015; 167: 87-94.
9. CAVALLI G, KOENDERS M, KALABOKIS V *et al.*: Treating experimental arthritis with the innate immune inhibitor interleukin-37 reduces joint and systemic inflammation. *Rheumatology* 2016; 55: 2220-2229. Erratum in: *Rheumatology* 2017; 56: 2256.
10. BRIZI MG, GALEAZZI M, LUCHERINI OM, CANTARINI L, CIMAZ R: Successful treatment of tumor necrosis factor receptor-associated periodic syndrome with canakinumab. *Ann Intern Med* 2012; 156: 907-8.