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

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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 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 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), erythrosedimentation 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-1β, 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 attempt 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.

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-TR APS (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
Adbominal 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 edema, %			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.

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