IL-17A as potential novel biomarker and promising therapeutic target in Kawasaki disease patients

Sirs,

Evidence emerging from recent studies has suggested that the interleukin 17 (IL-17) family cytokines may play a crucial role in the pathogenesis of Kawasaki disease (KD) since significantly higher IL-17A plasma concentrations have been detected in the KD population before intravenous immunoglobulin administration, particularly among those with coronary arteries abnormalities (CAA), in comparison to febrile controls (1, 2).

In this context, we reported similar results within our KD cohort when compared to patients with multisystem inflammatory syndrome in children (MIS-C).

To detect potential specific biomarkers, we systematically collected serum samples from 10 KD cases and 23 MIS-C patients at onset, before receiving any immunomodulatory treatment. The simultaneous measurement of pro-inflammatory cytokines and chemokines serum levels was assessed by Luminex Multiplex assay.

Upon comparing IL-17A levels between the two groups, a significantly higher median value was observed in KD patients compared to those with MIS-C (2.79 *vs*. 1.28 pg/mL, p=0.006). Intriguingly, KD patients also exhibited significantly higher median values of IL-6 (26.96 *vs*. 3.82 pg/mL, p=0.025), IL-5 (6.72 *vs*. 1.58 pg/mL, p=0.003), and IL-12p40 (85.34 *vs*. 16.97 pg/mL, p<0.001) levels compared to MIS-C (Fig. 1).

In our bivariate analysis, a positive correlation between IL-17A levels and alanine transaminase levels (ρs =0.727, p=0.027), as well as fibrinogen levels (ρs =0.883, p=0.008) was reported in the KD group. Furthermore, a strong positive correlation was detected between IL-17A and C-reactive protein levels in KD patients (ρs 0.922, $p\leq0.001$), suggesting a significant implication of this biomarker in the development of systemic inflammation. However, no significant correlations were found between clinical manifestations, particularly CAA, and IL-17A levels in our KD patients' group.

Additionally, the receiver operating characteristic (ROC) curve analysis using a cut-off defined by the Youden index showed that IL-17A demonstrated an acceptable performance in discriminating between KD and MIS-C (area under the curve [AUC]=0.76; 95% confidence interval [95%CI] 0.59–0.93, p=0.017).

At this regard, Brodeur *et al*. previously reported that IL-17A exhibited high sensitivity and specificity in distinguishing KD patients (n=23) from febrile controls, with an area under the ROC curve of 0.95 (95% confidence interval 0.89–1.00) (2). These findings confirm the potential role of IL-17 family cytokines as specific biomarkers for diagnosing KD, even though a different assay method, the Proximity Extension Assay (PEA) technology, was adopted.

This evidence suggests that the elevation of IL-17 family cytokines could emerge as a hallmark of KD and allow for distinguishing KD from its clinical mimics. IL-17A could represent a sensitive and promising biomarker for diagnosing KD, as plasma levels were found to be elevated at KD onset in various groups of KD patients despite the use of different assay methods. Therefore, good reproducibility and consequently wide potential application in clinical practice could be hypothesised.

Another important implication is the possibility of new therapeutic strategies. Currently, monoclonal antibody therapies targeting IL-17 are used to treat several chronic rheumatologic diseases, primarily in adults. Secukinumab and ixekizumab, have been approved for the treatment of psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) in adults, as well as paediatric psoriasis. Additionally, secukinumab has recently been approved for treating paediatric patients with enthesitis-related arthritis (ERA) and juvenile PsA (JPsA). If the role of IL-17 will be definitively confirmed as a key mediator in the pathogenesis of KD, this class of drugs may represent a novel therapeutic option, especially in the clinical context of KD refractory to conventional treatments.

Further studies involving larger patient cohorts are necessary to validate these results, define specific reference cut-off values, and evaluate the variation in plasma values of this proinflammatory cytokine in relation to CAA and before and after different therapeutic regimens.

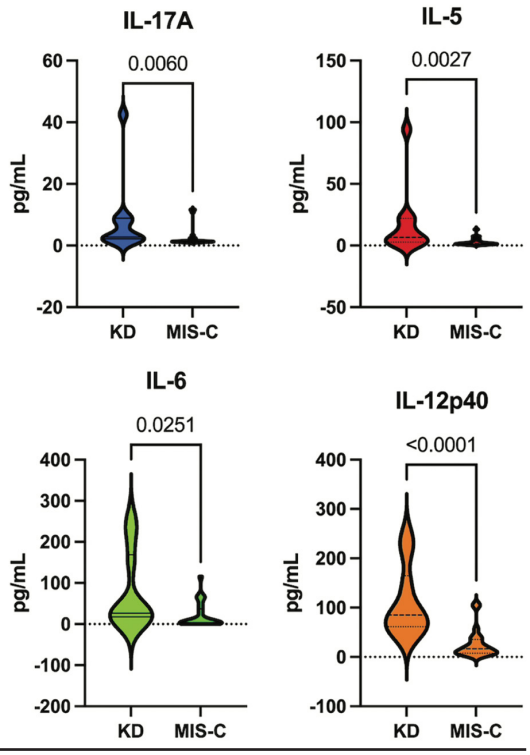

Fig. 1. Comparison of cytokine levels in Kawasaki disease (KD) and multisystem inflammatory syndrome in children (MIS-C) patients.

M.V. Mastrolia[1,2], *MD*
E. Ferraro[3], *BS*
E. Marrani[1], *MD*
L. Gatti[1], *MD*
M. Moriondo[3], *BS*
G. Simonini[1,2], *MD*

[1]Rheumatology Unit, ERN ReCONNET Center, Meyer Children's Hospital IRCCS, Firenze; [2]Neurofarba Department, University of Florence; [3]Laboratory of Immunology and Molecular Microbiology, Meyer Children's Hospital IRCCS, Firenze, Italy.

Please address correspondence to:
Maria Vincenza Mastrolia
Rheumatology Unit, ERN ReCONNET Centre, Meyer Children's Hospital IRCCS,
Viale Gaetano Pieraccini 24,
50139 Firenze, Italy.
E-mail: maria.mastrolia@unifi.it

Funding: this study was supported in part by funds from the 'Current Research Annual Funding' of the Italian Ministry of Health.

Competing interests: none declared.

References

1. LIN IC, SUEN JL, HUANG SK *et al*.: Involvement of IL-17 A/IL-17 Receptor A with neutrophil recruitment and the severity of coronary arteritis in Kawasaki disease. *J Clin Immunol* 2024; 44(3): 77. https://doi.org/10.1007/s10875-024-01673-1
2. BRODEUR KE, LIU M, IBANEZ D *et al*.: Elevation of IL-17 cytokines distinguishes Kawasaki disease from other pediatric inflammatory disorders. *Arthritis Rheumatol* 2024; 76(2): 285-92. https://doi.org/10.1002/art.42680