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ORIGINAL ARTICLE

Analysis of proinflammatory cytokine responses in Takayasu arteritis

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ABSTRACT

Objectives: This study aimed to investigate the expression of proinflammatory cytokines under long-term T helper (Th) 17 cell inducing conditions in Takayasu arteritis (TAK), a granulomatous vasculitis with adaptive immune responses.

Patients and methods: This cross-sectional study was conducted between May 2014 and April 2017. Peripheral blood mononuclear cells from 25 patients (23 females, 2 males; mean age: 42.7±15.5 years; range, 20 to 69 years) with TAK and 25 healthy controls (HCs; 11 females, 14 males; mean age: 39.1±9.3 years; range, 21 to 64 years) were cultured in Th17 cell-inducing conditions for six days. Cultured cells were stained with conjugated monoclonal antibodies to determine the intracellular cytokine secretion by flow cytometry. Supernatant samples were measured with sandwich enzyme-linked immunosorbent assay for interferon-gamma (IFN-γ), interleukin (IL)-17, IL-7, IL-21, and IL-22 levels.

Results: Under Th17 cell-inducing conditions, IFN-γ secretion was significantly higher in the TAK group compared to HCs ($p<0.005$). Unstimulated serum cytokine levels showed no differences between the TAK and HC groups, except for IL-7. Both IL-17 and IFN-γ secretion showed significant increases in TAK and IL-17 secretion in HCs in comparison of unstimulated and stimulated samples for each individual (p values, 0.022, 0.005, and 0.016, respectively). The production of IL-17 and IFN-γ by $CD4^+$, $CD8^+$, and $γδ^+$ T cells and B cells was not found to be significantly different between TAK patients and HCs. No differences were observed between the subgroups of TAK according to disease activity or treatment in IL-17 and IFN-γ production.

Conclusion: This study supports cell-mediated cytotoxicity as the main pathogenetic mechanism of TAK. T cells express higher levels of IFN-γ in TAK but not IL-17. Supernatant analysis indicated significantly higher IFN-γ production, which significantly increased after induction, suggesting the contribution of different inflammatory cells (probably $CD8^+$ and $γδ^+$ T cells) to IFN-γ production in TAK.

Keywords: Adaptive immunity, interferon-gamma, interleukin-17, Takayasu arteritis, T helper 17 cells.

Takayasu arteritis (TAK) is an idiopathic chronic granulomatous vasculitis of the aorta and its main branches with segmental involvement. TAK affects young females in 80 to 90% of cases, and vessel inflammation may lead to segmental stenosis, occlusion, dilatation, or aneurysm formation.[1] TAK is mainly driven by cell-mediated immune response with infiltrating cells consisting mainly of $γδ^+$ T lymphocytes, natural killer (NK) cells, macrophages, $CD8^+$ cytotoxic T lymphocytes, $CD4^+$ T helper (Th) 1 cells, multinucleated giant cells, and granulocytes.[2,3] Cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha, interleukin (IL)-6, and IL-18 were observed in higher levels in TAK, and IL-6 and IL-18 in particular were also correlated with disease activity.[4,5] The role of Th17 cell responses was also suggested in TAK, and IL-17 production was correlated with the development of large vessel arteritis more recently.[3,4,6,7] Additionally, with further studies, Th17-related immunity has been turned to a common title with the shown effect of several cytokines

having role in the transcription, production, regulation, and survival of Th17 cells. The main cytokines grouped under Th17-related immunity are IL-17, IL-21, IL-22, and IL-23.[3,4,7]

This study aimed to investigate the expression of Th1- and Th17-related immunity in TAK and the expression of proinflammatory cytokines, mainly IL-17 and IFN-γ, under long-term Th17 cell-inducing conditions.

PATIENTS AND METHODS

This descriptive, experimental, cross-sectional study was conducted at the Marmara University Faculty of Medicine Department of Rheumatology between May 2014 and April 2017. The study population included two groups: patients with TAK and healthy controls (HCs). The TAK group consisted of 25 consecutive patients (23 females, 2 males; mean age: 42.7±15.5 years; range, 20 to 69 years) fulfilling the 1990 American College of Rheumatology criteria for the classification of TAK.[8] The disease activity was assessed according to the criteria defined by the National Institute of Health.[9] Eight patients were in the active phase (aTAK), 17 patients were in the inactive phase (iaTAK), and 18 were under immunosuppressive (IS) treatment. Blood samples from 25 HCs (11 females, 14 males; mean age: 39.1±9.3 years; range, 21 to 64 years) were obtained who were spouses of patients without a history of consanguineous marriage, TAK, or clinical manifestations of any other inflammatory diseases. We wanted to eliminate environmental factors between groups via this approach. The study protocol was approved by the Marmara University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (date 23.02.2012, decision no: 09.2012.0026). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Heparinized venous blood (2 mL) was collected from participants and peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll-Paque density gradient separation. Isolated PBMCs were suspended in a complete RPMI medium. While 1×10^6 cells were left unstimulated, 1×10^6 cells were kept at Th17 cell-inducing conditions for the long term, as previously defined.[10] Th17 cell induction was maintained for six days with the addition of 30 ng/mL of IL-6, 5 µg/mL of phytohemagglutinin (PHA), 10 ng/mL of IL-1β, and 10 ng/mL of IL-23 on Day 0. All stimulated and unstimulated cells were transferred to culture plates and put into a 5% carbon dioxide incubator at 37°C. On the second day of incubation, 10 ng/mL of IL-23 was added to stimulated samples. On the fifth day of incubation, 5 µg/mL of PHA, 10 µg/mL of brefeldin A, 20 ng/mL of phorbol 12-myristate 13-acetate (PMA), and 10 ng/mL of IL-23 were added into stimulated samples, whereas only 10 µg/mL of brefeldin A and 20 ng/mL of PMA were added into unstimulated samples. On the sixth day, samples were washed to separate cellular components and supernatants.

The concentrations of IL-7, IL-17, IL-21, IL-22, and IFN-γ in supernatants under unstimulated and stimulated conditions were measured with 96-well plates and commercial sandwich enzyme-linked immunosorbent assay (ELISA) kits following the manufacturer's instructions (Invitrogen; Thermo Fisher Scientific, Waltham, MA, USA). All concentrations were reported in pg/mL.

Cultured PMBCs were stained with the following conjugated monoclonal antibodies to determine T and B cell subsets: CD4-PECy7, CD8-APC-Cy7, CD3-PerCp, TCR gamma/delta-APC, CD19-PerCp, IFN-γ-FITC, and IL-17-PE (BD Biosciences, San Jose, CA, USA). PBMCs were then fixed and permeabilized using a Cytofix/Cytoperm Plus kit (BD Biosciences, San Jose, CA, USA) according to the manufacturer's instructions. For intracellular cytokine detection, antibodies were used. Data were acquired using a FACSCanto flow cytometer with Diva software version 7.0 (BD Biosciences, San Jose, CA, USA) and analyzed with the FlowJO version 10.0 (TreeStar Inc., San Carlos, CA, USA) software. The quantitative values were presented as the percentages of the given cell subgroups among the total cell population.

Statistical analysis

Data were analyzed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA), Graphpad Prism version 5.0

(GraphPad Software Inc., La Jolla, CA, USA), and Minitab version 17.1.0 (Minitab Inc., State College, PA, USA). Data were presented as mean ± standard deviation (SD) for continuous variables and as percentages for qualitative variables. Considering the distribution and sample size of groups, the difference between groups was analyzed by the nonparametric Mann-Whitney U test for independent variables. The Wilcoxon test was used for paired continuous variables. Multiple comparisons were conducted with the independent sample Kruskal-Wallis test with Bonferroni correction. A p-value <0.05 was considered statistically significant.

RESULTS

There was no significant difference between the mean ages of the TAK and HC groups (p=0.159). The comparison of IL-7, IL-17, IL-21, IL-22, and IFN-γ secretion on supernatants was evaluated with the sandwich ELISA method. The comparisons of the TAK and HC groups and stimulated and unstimulated samples in each group are presented in Table 1. Under Th17 cell-inducing conditions, IFN-γ secretion was significantly higher in the TAK group compared to HCs and unstimulated samples of TAK patients (p=0.005 for both).

Unstimulated serum cytokine levels showed no significant differences between the TAK and HC groups, except for IL-7 (p=0.022). In the comparison of unstimulated and stimulated samples for each groups, both IL-17 and IFN-γ secretion showed a significant increase in the TAK group, and IL-17 secretion showed a significant increase in HCs (p=0.005 and p=0.016, respectively).

Under Th17 cell-inducing conditions, IL-17 expression from $CD4^+$, $CD8^+$, and $\gamma\delta^+$ T cells and B cells was not significantly different between the TAK and HC groups (Figure 1, Table 2). Under Th17 cell-inducing conditions, expression of IFN-γ by $CD4^+$, $CD8^+$, and $\gamma\delta^+$ T cells and B cells was not statistically different between the two groups. The effect on

Table 1. Analysis of cytokine production via ELISA for the TAK and HC groups

	TAK group			HC group			
	n	Median	Min-Max	n	Median	Min-Max	*p* value
IL-17 US	10	4	0-99	13	28	1-209	0.420
IL-17 PHA	12	93	0-1170	13	171	4-398	0.166
p value**		**0.022**			**0.016**		
IFN-γ US	10	31	11-238	13	68	0-291	0.392
IFN-γ PHA	12	571	21-1260	13	88	14-838	**0.005**
p value**		**0.005**			0.162		
IL-7 US	10	20.5	3-81	13	11	4-43	**0.003**
IL-7 PHA	12	14.5	6-82	13	28	4-119	0.777
p value**		0.444			0.136		
IL-21 US	10	10.5	2-24	12	8	3-83	0.191
IL-21 PHA	12	15.5	7-496	13	8	4-32	**0.049**
p value**		0.066			0.668		
IL-22 US	10	58	30-199	13	35	24-103	0.385
IL-22 PHA	12	96	30-187	13	63	34-1100	0.150
p value**		0.074			0.055		

ELISA: Enzyme-linked immunosorbent assay; TAK: Takayasu's arteritis; HC: Healthy controls; IL: Interleukin; IFN-γ: Interferon-gamma; US: Unstimualted; PHA: Phytohemagglutinin; * Mann-Whitney U test for the comparison of TAK and HC groups; ** Wilcoxon test for the comparison of US *vs.* PHA measurements of given cytokine.

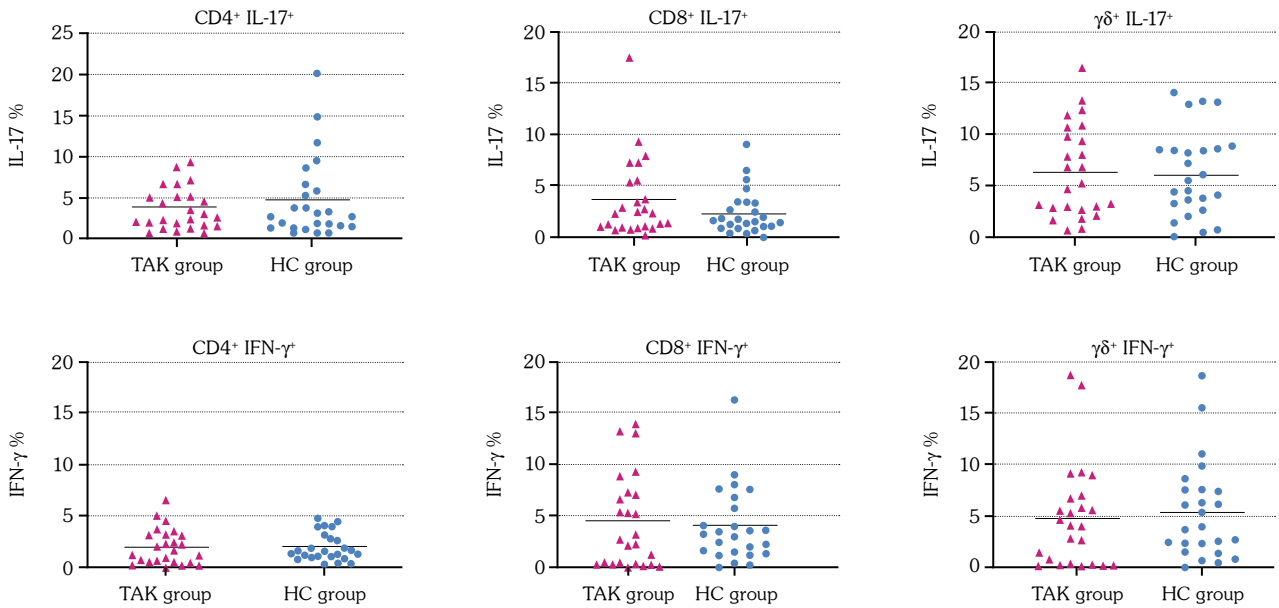

Figure 1. IL-17 and IFN-γ expression in TAK patients and HC groups. Under Th17 inducing conditions, IL-17 (upper row) and IFN-γ (lower row) expression from CD4⁺, CD8⁺ T cells, and γδ+T cells were not found to be significantly different between TAK and HCs.

IL: Interleukin; IFN-γ: Interferon-gamma; TAK: Takayasu's arteritis; HCs: Healthy controls

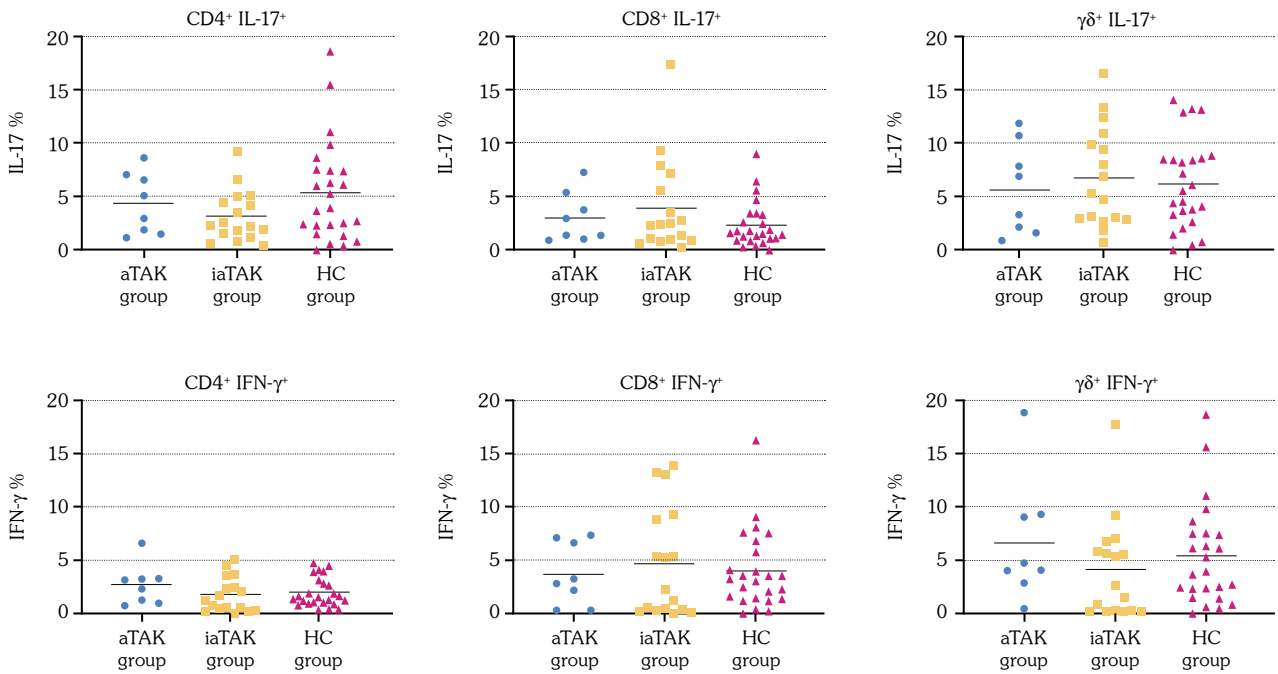

Figure 2. IL-17 and IFN-γ expression in TAK patients according to disease activity. The effect on disease activity in the expression of IL-17 (upper row) and IFN-γ (lower row) showed no significant differences between active TAK and inactive TAK patient subgroups, and HCs.

IL: Interleukin; IFN-γ: Interferon-gamma; TAK: Takayasu's arteritis; HCs: Healthy controls.

Table 2. IL-17 expression and IFN-γ production in TAK patients and HCs according to treatment status or disease activity

	All TAK (n=25)	IS TAK (n=18)	Non-IS TAK (n=7)	Active TAK (n=8)	Inactive TAK (n=17)	HC (n=25)
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
$CD4^+$ $IFN\text{-}\gamma^+$	2.02±1.7	2.00±1.9	2.08±1.3	2.65±1.9	1.73±1.6	1.96±1.4
$CD4^+$ $IL\text{-}17^+$	3.54±2.5	3.22±2.2	4.35±3.3	4.35±2.8	3.15±2.4	4.55±4.9
$CD8^+$ $IFN\text{-}\gamma^+$	4.37±4.5	4.67±5.0	3.60±2.9	3.71±2.9	4.69±5.1	4.00±3.6
$CD8^+$ $IL\text{-}17^+$	3.63±3.9	3.69±4.4	3.48±2.2	3.00±2.3	3.93±4.5	2.36±2.2
$\gamma\delta^+$ $IFN\text{-}\gamma^+$	4.87±5.0	4.09±4.6	6.87±5.8	6.61±5.7	4.05±4.6	5.38±4.7
$\gamma\delta^+$ $IL\text{-}17^+$	6.38±4.5	6.55±4.8	5.96±3.7	5.65±4.3	6.73±4.6	6.16±4.2

IL-17: Interleukin 17; IFN-γ: Interferon gamma; TAK: Takayasu arteritis; HC: Healthy controls; SD: Standard deviation; IS: Immunosuppressed. Subgroup analysis with Bonferroni correction showed significant differences between these subgroups for given parameters.

disease activity of IL-17 and IFN-γ expression was analyzed, and there were no significant differences between the aTAK and iaTAK subgroups (Figure 2, Table 2). Additionally, both the aTAK group and the iaTAK group was similar to HCs regarding expression of IL-17 and IFN-γ. When the subgroup analysis of IL-17 and IFN-γ expression was performed according to IS use, there were no significant differences between IS and non-IS TAK patient subgroups or TAK subgroups and HCs (Table 2).

DISCUSSION

Although IL-6 appears to be the cytokine best associated with activity in TAK, many other proinflammatory and anti-inflammatory cytokines are increased in TAK.[11,12] In this study, we evaluated the role of both Th1- and Th17-mediated immunity and the expression of IFN-γ and IL-17 both on unstimulated and stimulated cell culture supernatants and also from several types of T and B cells. To better understand Th17-related immunity, we analyzed IL-17 as the cytokine marker, other members of Th17-related immunity, including IL-21 and IL-22, and IL-7 as the regulatory cytokine. Our results showed that TAK patients secreted increased levels of IFN-γ under Th17 cell-inducing conditions, whereas the Th17 cell responses were limited.

Previous studies examined PBMCs upon stimulation and found predominant Th1 and Th17 cell responses.[3] Compared to other studies in the literature investigating Th17 cell responses, there are some methodological differences in our study. In most studies, stimulation periods with PMA or other stimulators lasts 4 to 6 h, whereas similar to our previous study in patients with Behçet's disease, we performed long-term (six days) induction in this study.[3,10,13,14] In this setting, we added PMA on the fifth day of culture 24 h before the completion of the cultivation period, which is much later than the well-known culture protocols. Furthermore, although the induction of $CD4^+$ T cells is usually performed with anti-CD3, anti-CD28, and IL-2 and either IL-1β or IL-6 is used for Th17 cell differentiation, we added IL-23, IL-6, and IL-1β on Day 0 of culture.[3,13-16] Consequently, this study aimed to show mainly IL-17-related immune responses with longer stimulation and hypothesized that these *in vitro* conditions would better imitate *in vivo* conditions, as innate and adaptive immune cells are activated together for longer periods *in vivo* in immune-mediated disorders.

Takayasu arteritis is mainly a disorder of adaptive immunity. The main response in TAK is shown to be cell-mediated cytotoxicity, as infiltrating cells such as $\gamma\delta^+$ T cells, NK cells, and cytotoxic T cells in the aortic tissue act as perforin-expressing killer cells and directly injure the vascular cells by secreting numerous perforin molecules.[17] $CD8^+$ T cells are one of the major cell types among those perforin-expressing killer cells and infiltrate the arterial wall by producing

cytotoxic molecules, specifically granzymes and perforin, and cytokines, specifically IL-17 and IFN-γ.[18]

IFN-γ is the prototype Th1-mediated cytokine and is widely investigated in the pathogenesis of TAK and granuloma formation.[19] Several cell types have the potential to secrete IFN-γ, with the predominance of Th1 and NK cells. The source of IFN-γ was also investigated, and Ren et al.[19] suggested $CD8^+$ T cells as one of the major sources of IFN-γ in TAK patients.[18] Therefore, consistent with the literature, even if not statistically significant, our findings suggested that IFN-γ secretion was mainly driven by $CD8^+$ T cells and $\gamma\delta^+$ T cells.[19] The most prominent genetic association of TAK was shown to be HLA (human leukocyte antigen)-B52, which, as a class I allele, might be linked to increased $CD8^+$ T cell responses.[20] On the other hand, although flow cytometer analysis showed this tendency, overall IFN-γ production in supernatant, reflecting the cumulative contribution of all cell types, pointed out a significantly higher amount of IFN-γ compared to both HC and unstimulated internal controls of TAK. Therefore, the entire analysis of our results suggested that $CD8^+$ T cells might not be the only major source of IFN-γ production, particularly under PHA induction in the TAK group, and basic analysis with flow cytometer gives limited information to describe all components of this inflammatory response.

Th17 cells, the $CD4^+$ T cell subset that secretes IL-17, are pathogenic in autoimmune diseases, and their development and expansion are driven by the cytokines IL-6, tissue growth factor-beta, IL-21, IL-1, and IL-23. While $CD4^+$ and $CD8^+$ T cells are important sources of this cytokine, $\gamma\delta^+$ T cells and several families of innate lymphoid cells can also secrete IL-17 as innate sources of IL-17 with IL-1β and IL-23 stimuli.[11,21,22] Saadoun et al.[3] suggested the role of IL-17 and Th17 cells in the sera and vascular specimens of TAK patients, but our findings did not show such a significant difference in the TAK group. We believe that this response is much more limited in TAK compared to innate immunity-driven diseases, such as Behçet's disease. On the other hand, the comparison of serum levels of IL-17 was 93 pg/mL *vs.* 171 pg/mL in the TAK and HC groups, respectively. The level of IL-17 after stimulation was lower in the TAK group. However, in both groups, there was a significant increase in comparison to unstimulated internal controls. However, we might speculate about a more prominent response to stimulation in the TAK group, and the increase after stimulation was more prominent in the TAK group with a 23.25-fold increase (from 4 to 93 pg/mL) compared to the HC group's 6.1-fold increase (from 28 to 171 pg/mL). Therefore, the main difference could be related to the large number of iaTAK patients among the TAK group, which could have caused lower baseline IL-17 levels.

The association of IL-17 and IFN-γ with disease activity in TAK was also analyzed in the current study, and no differences were shown between patients in active and remission status. Similarly, IS treatments did not influence the secretion of IL-17 by PBMCs in TAK patients.[3,7] On the other hand, the role of IFN-γ in TAK disease activity is controversial. Some studies found no difference between patients in active and remission status, whereas IFN-γ was higher in active disease in other studies.[3,11,23,24] However, the role of IFN-γ in TAK as a Th1 cell signature appears to be clear, and in several studies, upon stimulation, $CD4^+$ and $CD8^+$ T cells have been associated with increased IFN-γ expression, as in our study.[3,11,12]

In a recent approach, a newer group of Th17 cells, named Th17.1 cells were defined, and they have been shown to dually secrete IL-17 and IFN-γ.[25] The role of these newer cell groups in TAK have also been evaluated and associated with TAK disease activity. In our study, we analyzed only common markers of Th17 cells.[26] Cells without a subgroup analysis but the dual secretion of the two prototype cytokines of TAK from this special cell group is also noteworthy for understanding adaptive immunity and lymphocyte-driven immune response in TAK.

Interleukin-7 contributes to the development of pre-B and pre-T cells and their survival.[27] Its regulatory effects have also been shown on IL-17 producing $\gamma\delta^+$ T cells, and it may have the potential to affect both innate and adaptive inflammatory responses.[28] In several autoimmune diseases, including rheumatoid

arthritis, psoriasis, and primary Sjögren syndrome, increased levels of IL-7 were shown.[28-31] Similar to our findings, PBMCs from TAK patients were found to produce significantly higher levels of IL-7 in culture supernatants compared to HCs, displaying its role in stimulating lymphopoiesis in relation to the lymphocyte-mediated pathogenesis of TAK.[3]

Interleukin-21 is one of the cytokines associated with the pathogenesis of autoimmune disorders, and while its main source is Th cells, it is also expressed in NK cells, B cells, and $CD8^+$ T cells.[32] IL-22 is a cytokine that is produced by Th17 cells, $\gamma\delta^+$ T cells, NK cells, and innate lymphoid cells.[33] The major properties of IL-22 are related to modulator effects on tissue protection, survival, differentiation, and remodeling, with proinflammatory effects to a lesser extent.[32,34,35] Higher IL-21 levels are found in TAK patients, associated with more extensive arterial involvement, mainly sourced from follicular Th and Th17 cells. Similarly, higher IL-22 levels in TAK were associated with increased proinflammatory activity and ischemic events, either with a reparative role or as a result of proinflammatory stimulus.[35] Although not reaching significance, our results showed that Th17 cell-inducing conditions increase IL-21 and IL-22 levels in TAK groups compared to unstimulated samples.

The limitations of the study were the relatively small number of patients in subgroups and the presence of sex inequality, with female predominance in the TAK group. Additonally, we evaluated Th17 cells without a subgroup analysis. In further studies, Th17 subgroups analysis including Th17.1 cells can be conducted.

In conclusion, our results suggest that under long-term Th17 cell-inducing conditions, T cells express higher levels of IFN-γ in TAK patients but not IL-17. While the primary source of IFN-γ was likely $CD8^+$ and $\gamma\delta^+$ T cells, they may not be the only source. These findings support the role of cell-mediated immune response in the pathogenesis of TAK.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: R.D., H.D.; Design: R.D., A.T.V., F.T.Ö., H.D.; Control/supervision, references and fundings: H.D; Data collection and/or processing: R.D., A.T.V., F.T.O., A.U.Ö., G.Ö., F.A.Ö., I.A.T.; Analysis and/or interpretation: R.D., A.T.V., H.D.; Literature review, writing the article: R.D.; Critical review: A.T.V., H.D.; Materials: R.D., A.T.V., F.T.O., A.U.Ö., G.Ö., F.A.Ö., I.A.T., H.D.

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