The Turkish Journal of Pediatrics 2022; 64: 228-238
https://doi.org/10.24953/turkjped.2021.83

Original Article

Regulatory T and B cells in transient hypogammaglobulinemia of infancy

Ayça Emsen, Hülya Uçaryılmaz, Tuğba Güler, Hasibe Artaç

Division of Immunology and Allergy, Department of Pediatrics, Selcuk University Faculty of Medicine, Konya, Turkey.

ABSTRACT

Background. Transient hypogammaglobulinemia of infancy (THI) is a heterogeneous disorder caused by an abnormal delay in reaching normal IgG levels in the first three years of life. Although THI is a common primary immune deficiency, its pathogenesis has not been fully elucidated. We aimed to investigate the role of regulatory T cells (Tregs) and B cells (Bregs) in the pathogenesis of THI.

Methods. T and B cell subsets were evaluated in 40 patients with THI aged 6–41 months and 23 healthy controls aged 6–51 months using flow cytometry. CD4 and interleukin-2 receptor-α alpha (CD25) expression and a lack of interleukin-7 receptor-α (CD127) were used for Treg identification. FoxP3 expression in Tregs was determined as a percentage and mean fluorescence intensity. B cell subsets (plasmablast, mature naive, primarily memory, new memory) and Bregs were defined according to CD19, CD38, and CD24 expressions.

Results. Patients with THI (15 females and 25 males; mean age: 18.8 ± 8.6 months) and controls (10 females and 13 males; mean age: 22.6 ± 13.1 months) participated in this study. While the proportion of Tregs of children with THI were significantly increased compared to the controls, primarily memory B cells were reduced. Additionally, the proportions of CD127 in $CD3^+$ and $CD3^+CD4^+$ T cells were significantly reduced in the patients with THI compared to the control. No significant difference was detected in the FoxP3 expression of Tregs and the frequency of Bregs in the children with THI.

Conclusions. Increased Tregs and decreased primarily memory B cells may cause antibody production delay in children with THI. Changes in the T and B cell compartments may be related to chronic immune activation and affected cellular immunity in THI. Further studies are needed to use T and B cell subsets in the prediction of IgG level recovery.

Key words: transient hypogammaglobulinemia of infancy, regulatory T cells, regulatory B cells.

Transient hypogammaglobulinemia of infancy (THI) is a primary immune deficiency disease that is a subclass of predominantly antibody deficiencies.[1] THI is characterized by prolongation of the physiological hypogammaglobulinemia period due to the delay in the production of immunoglobulin (Ig).[2] In THI, mainly IgG levels, prevalently IgA and IgM levels, are lower than two standard deviations (SDs).[3] Although the actual incidence of this disease is unknown because most patients are asymptomatic and severe infections are rare, different results have been reported in studies of various centers.[3-6] According to Kılıç et al.[5], 73.9% of primary immunodeficiencies were primary antibody deficiencies, and THI constituted 31% of primary antibody deficiencies (22.9% in primary immunodeficiencies) in Turkey.

Clinically, THI is characterized by recurrent lower respiratory tract infection (LRTI) and upper respiratory tract infection (URTI), urinary tract infections, gastroenteritis, and invasive infections.[3] THI can be distinguished from other immunodeficiencies by its intact cellular

✉ Hasibe Artaç
artachasibe@gmail.com

Received 14th January 2021, revised 6th May 2021, 27th July 2021, 9th October 2021, accepted 24th November 2021.

This study was presented as an oral presentation at the 1st International Rumi Pediatric Congress, 4-7 December 2019, Konya, Turkey.

immunity, protective antibody response, and clinical improvement in serum Ig levels.[6] Spontaneous clinical improvement occurs in the 9th–15th month, but normalization of IgG levels can be delayed up to 2-5 years of age.[7]

The cause of the immune system disorder leading to hypogammaglobulinemia has not been fully understood in THI.[8] Studies have reported reasons for low Ig levels in THI as abnormalities in the B cell compartment, decreased numbers of the CD19 complex and memory B cells, defects in T helper cell (Th) maturation and function, aberrant cytokine production, and increased number of regulatory T cells (Tregs) and myeloid-derived suppressor cells.[6,9-13]

In studies involving children with THI, it has been reported that antibody production deficiency is associated with delayed maturation of Th cells.[6] IL-2 receptor-α (CD25) and IL-7 receptor-α (CD127) play an essential role in T cell development and antigen-specific T cell responses. As a result of the binding of IL-7 to its receptor (CD127), antiapoptotic molecules upregulate in T cells, and the T cell receptor–mediated signaling pathway initiates, leading to IL-2 production and proliferation in newly activated T cells. After activation by antigens and IL-7 binding, T cells lose CD127 surface expression. Therefore, CD127 is used to distinguish between effector, memory, and regulatory T cells.[14] $CD25^{+}CD127^{low/-}$ cells (Tregs) have regulatory functions and play an essential role in suppressing excessive inflammatory responses, preventing reactions to harmless environmental molecules, and suppressing the autoantibody response to self-antigens.[15,16]

$CD19^{+}$ B cell subsets at different maturation stages have been defined according to their CD38 and CD24 expressions.[17] CD38 is a coreceptor in mature B cells and leads to apoptosis in early B cells while increasing survival in B cells derived from the lymph node germinal center.[18] CD24 is a cell surface receptor responsible for regulating the maturation stage of B cells in the bone marrow, similar to CD38.[19] Together with the B cell receptor, CD24 functions in the apoptosis of autoreactive B cells. CD24 can regulate B cell receptor–mediated B cell selection in the bone marrow, thereby producing and leading to the migration of regulatory B cells (Bregs).[20] Bregs ($CD19^{+}CD38^{hi}CD24^{hi}$ B cells) regulate T and B cell responses, including the maintenance of Tregs.[21,22] The functions of Bregs have been demonstrated in autoimmunity, allergy, infections, and cancer.[22-24] Inborn errors of immunity associated with Breg deficiency have not been described so far. However, a decrease in $CD19^{+}CD38^{hi}CD24^{hi}$ B cells (Bregs) of patients with common variable immune deficiency has been reported.[25,26]

Although B cells have often been investigated due to hypogammaglobulinemia in THI, the role of Bregs is unclear. In this study, we investigated Tregs and Bregs to elucidate the immunological mechanisms causing hypogammaglobulinemia in children with THI.

Material and Methods

Study participants

Forty patients diagnosed with THI aged 6–41 months and 23 healthy controls aged 6–51 months were included in this study. Informed consent was obtained from the parents of the children with THI before they were included in the study. This study was approved by the Ethical Committee of Selcuk University Medical Faculty (2015/265).

The diagnosis of THI was based on the following criteria: (i) low serum levels of mainly IgG (< 2 SDs below age-defined norms) with and/or without reduced IgA and IgM levels diagnosed in the first three years of life; (ii) normal vaccine responses, isohemagglutinins, peripheral blood lymphocyte subpopulations, and cellular immunity; and (iii) defined causes of hypogammaglobulinemia (such as other primary immunodeficiencies, genetic disorders, chromosomal abnormalities, and other systemic illnesses or drugs) were excluded.[3,27]

The initial indications for testing immunoglobulin levels were recurrent URTI and/or LRTI, recurrent otitis media, and gastroenteritis.[28] The patients' demographic data and clinical history (such as age, gender, types and frequency of infections in the last year, hospitalizations, and history of allergic diseases and other systemic diseases) were obtained from their medical records. Hemoglobin, leukocyte, lymphocyte, and platelet levels, as well as IgG, IgA, and IgM levels, were recorded on admission. Clinical observation was performed regularly every three months, and immunoglobulin levels were checked every six months. Infections and treatments (antibiotic prophylaxis, inhaled steroid, or intravenous immunoglobulin) of the patients were recorded during the follow-up.

Flow cytometric analysis

Peripheral lymphocyte subsets, Tregs, and Bregs in ethylenediamine tetra-acetate anticoagulated peripheral blood samples of the patients with THI and the control group were analyzed using FACSAria III flow cytometer (Becton–Dickinson, CA, USA) and FACSDiva version 6.1.3 software package. Peripheral blood mononuclear cells were isolated from heparinized blood using Ficoll-Histopaque density gradient centrifugation, and flow cytometric analysis of these cells was performed on at least 50,000 acquired events. Treg staining was performed using CD3 (APC), CD4 (PerCP), CD25 (PE), FoxP3 (Alexa fluor 488), and CD127 (Alexafluor 700) monoclonal antibodies (Biolegend, San Diego, USA). In the flow cytometric analysis, lymphocytes were gated, and then $CD25^{+}CD127^{low/-}$ Tregs, $CD25^{low/-}CD127^{+}$ T, and $CD25^{-}CD127^{-}$ T cells were identified at the $CD3^{+}CD4^{+}$ Th gate (Fig. 1A and 1B).[15] FoxP3 expression of $CD25^{+}CD127^{low/-}$ Tregs was determined as a percentage and mean fluorescence intensity (MFI).

B cell subsets were determined according to their expression at maturation stages using CD19 (FITC), CD24 (APC), CD38 (Alexa fluor 700) monoclonal antibodies (Biolegend, San Diego, USA) (Fig. 2).[29] At the $CD19^{+}$ B cell gate in the lymphocyte population, the $CD38^{hi}CD24^{hi}$ Bregs, $CD38^{int}CD24^{int}$ mature naive B cells, $CD38^{hi}CD24^{-}$ plasmablast, $CD38^{-}CD24^{+}$ primarily memory B cells, and $CD38^{-}CD24^{-}$ new memory B cells were determined (Fig. 3A).[30]

Statistical analysis

Statistical analysis of the data was performed using IBM SPSS for Windows 17.0 software package (IBM Corp, Armonk, NY, USA). Tregs and B cell subsets were determined and compared in the patients with THI and the control groups. Descriptive statistics such as the number of patients in the THI and control groups, geometric mean, arithmetic mean, minimum and maximum values, and mean ± 2 SD values were given for both groups. When

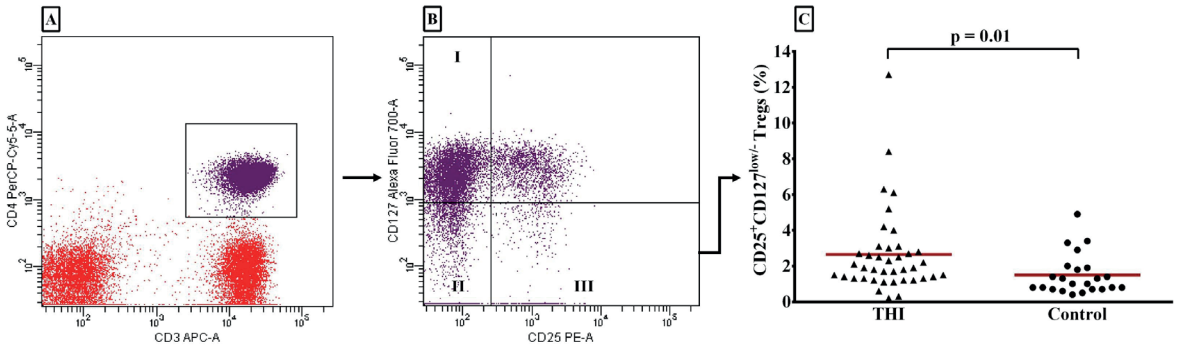

Fig. 1. Flow cytometric analysis of Tregs according to CD127 and CD25 expressions (A - B), statistically comparison of Tregs (C) in THI and control groups. $CD3^{+}CD4^{+}$ Th cells were classified as $CD25^{low/-}CD127^{+}$ T cells (I), $CD25^{-}CD127^{-}$ T cells (II) and $CD25^{+}CD127^{low/-}$ Tregs (III).

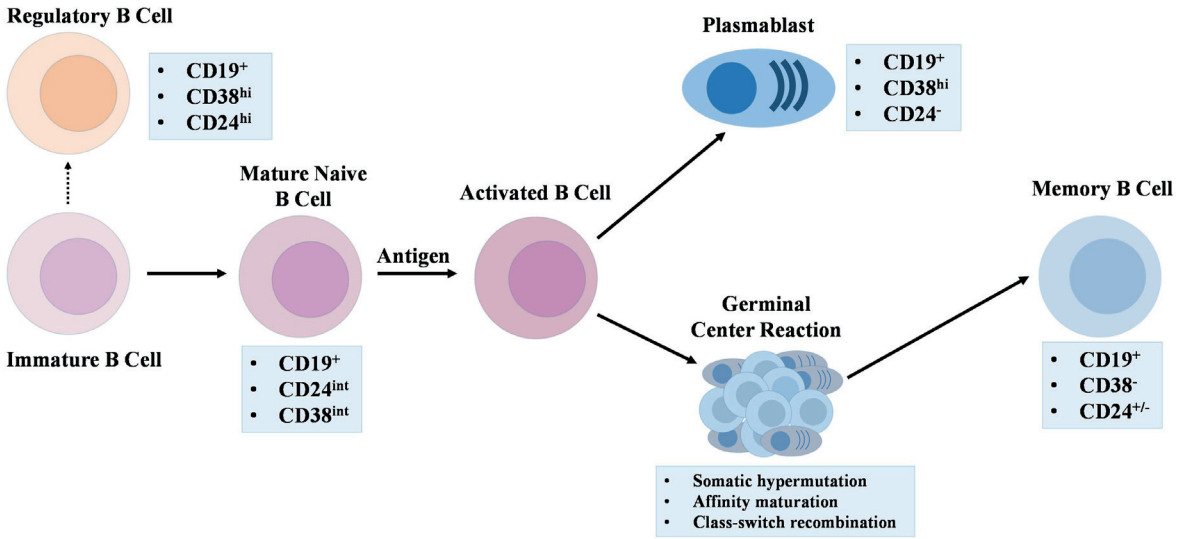

Fig. 2. B cell differentiation pathways and B cell subsets identified in this study. Immature B cells that develop in the bone marrow differentiate into regulatory B cells or mature naive B cells. Upon activation by antigen, mature naive B cells either give rise to plasmablasts or enter the germinal center reaction, in which somatic hypermutation, affinity maturation and class switch recombination to differentiate memory B cells.[29]

examining the differences in the comparison of means between two groups, the student t-test was used in independent groups for data showing normal distribution, while the Mann-Whitney U test was used for data without normal distribution. The significance level was accepted as $p < 0.05$.

Results

Demographic characteristics and clinical features of the study population

The THI group had 15 females and 25 males with a mean age of 18.8 ± 8.6 months (range: 6–41 months), while the control group consisted of 10 females and 13 males with a mean age of 22.6 ± 13.1 months (range: 6–51 months). There was no significant difference between the patient and control groups based on sex and age distribution.

When the clinical findings of the patients with THI were evaluated, the most common clinical presentations were recurrent URTIs in 24 patients (60%), LRTIs in 27 patients (67.5%), diarrhea in 10 patients (25%), urinary tract infection in 2 patients (5%), and allergic disease in 8 patients (20%). Twenty patients (50%) were hospitalized at least once due to infection. The main causes of hospitalization were acute bronchiolitis (70%), gastroenteritis (20%), and pneumonia (10%). Etiological agents were determined in 10 of 20 patients. *Rhinovirus*, *human metapneumovirus*, and *respiratory syncytial virus* were identified as causative pathogens of bronchiolitis cases. *Rotavirus* and *Streptococcus pneumonia* were detected as etiological agents for gastroenteritis and pneumonia cases, respectively. None of these patients had severe infections, including sepsis or meningitis. Four patients (10%) received intravenous IgG, and one of them had Kawasaki disease. Thirty-one patients with THI (77.5%) were taking antibiotic prophylaxis during months 2–29 (Table I). The serum levels for IgG reached age-matched normal values in the median age of 32 months (range: 24–58 months).

Laboratory studies

The laboratory findings of the study groups are shown in Tables II and III. Serum IgG, IgA, and IgM levels at diagnosis were 406.4 ± 119.1, 19.2 ± 14.9, and 62.1 ± 22.8 mg/dL, respectively. Twenty-eight patients (70%) had low IgA, and

23 patients (57.5%) had low IgM titers. There was no significant difference between the patients in the THI and those in the control group based on leukocyte, lymphocyte, platelet, and hemoglobin levels (p > 0.05) (Table II).

$CD3^+$ Total T cell, $CD3^+CD4^+$T cells, $CD3^+CD8^+$ cytotoxic T cells, $CD19^+$ B cells, $CD16^+56^+$ natural killer cell counts, and CD4/CD8 T cell ratio were within normal ranges according to age in patients with THI.[31] There was no significant difference between the patients in the THI group and the control group based on lymphocyte subsets (p > 0.05) (Table II).

In the CD127 expression of T cells, although the percentage of CD127 in $CD3^+$ T and $CD3^+CD4^+$ T cells reduced (p = 0.00, p = 0.00, respectively), the CD127 MFI of these cells increased in patients

Table I. Clinical features and treatment of the patients with THI.

	THI group (N = 40)	
	n	%
Clinical features		
LRTI	27	67.5
URTI	24	60
Diarrhea	10	25
Allergic symptoms	8	20
UTI	2	5
Treatment		
Antibiotic prophylaxis	31	77.5
Hospitalization	20	50
The use of IVIG	4	10

THI: transient hypogammaglobulinemia of infancy, LRTI: lower respiratory tract infections, URTI: upper respiratory tract infections, UTI: urinary tract infection, IVIG: intravenous IgG

Table II. Serum immunoglobulin levels and lymphocyte subsets in THI and control groups.

	THI		Control		p
	Mean ± SD	Min – Max	Mean ± SD	Min – Max	
IgG (mg/dl)	406.4 ± 119.1	169 - 575	640.1 ± 163.9	358 – 950	0.000*
IgA (mg/dl)	19.2 ± 14.9	6.7 – 81	48.9 ± 38.8	8.1 – 166	0.00**
IgM (mg/dl)	62.1 ± 22.8	19.8 – 152	78.1 ± 35.6	30.1 – 209	0.02**
WBC ($x10^9$)	9.1 ± 2.5	5.2 – 15.5	9.4 ± 2.7	6 – 16.4	0.76**
Lymphocyte					
%	56.0 ± 9.9	29 – 74	53.6 ± 11.6	34 – 76	0.38*
Absolute ($x10^9$)	5.1 ± 1.5	2.8 – 9	5.0 ± 1.7	2.6 – 8.9	0.55**
CD3					
%	65.9 ± 6.8	51 – 88	65.5 ± 7.3	49 – 77	0.91**
Absolute number	3261.5 ± 1094.5	1711 – 6686	3246.0 ± 1266.5	1328 – 6590	0.89**
$CD3^+CD4^+$ T cells					
%	42.3 ± 7.0	30.6 – 56.3	41.1 ± 9.2	26.1 – 59.1	0.49**
Absolute number	2083.2 ± 719.8	1151 – 4090	2078.7 ± 1015.0	703 – 4717	0.63**
$CD3^+CD8^+$ T cells					
%	19.9 ± 4.7	10.2 – 28	19.9 ± 4.4	10.4 – 26.8	0.96*
Absolute number	1002.0 ± 436.9	399 – 2429	963.7 ± 349.2	357 – 1687	0.72*
$CD19^+$ B cells					
%	23.3 ± 6.3	7.9 – 35.5	23.4 ± 6.3	14.1 – 36	0.68**
Absolute number	1215.2 ± 707.7	288 – 4089	1137.8 ± 526.1	616 – 2601	0.62**
$CD16^+CD56^+$ NK Cells					
%	6.7 ± 3.5	1.3 – 14.7	6.2 ± 4.3	0.5 – 18.0	0.27**
Absolute number	333.2 ± 264.1	44 – 1669	313.4 ± 227.8	110 – 782	0.45**

SD: standard deviation, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, WBC: white blood cell, * Independent sample t-test **Mann–Whitney U test

Table III. T and B cell subsets in THI and control groups.

	THI		Control		p
	Mean ± SD	Min – Max	Mean ± SD	Min – Max	
$CD3^+$ T cells					
CD127 (%)	82.46 ± 10.20	43.4 – 96.3	89.97 ± 7.95	66.3 – 97.2	0.00**
CD127 (MFI)	6574.3 ± 3471.3	1438 – 18537	5271.8 ± 3946.9	1458 – 20343	0.04**
$CD3^+CD4^+$ T cells					
CD127 (%)	77.6 ± 13.0	34.5 – 96.6	87.9 ± 9.7	58.1 – 96.1	0.00**
CD127 (MFI)	6114.8 ± 3207	1197 – 15962	4989.7 ± 3821	1335 – 19573	0.05**
$CD3^+CD4^+$T cell subsets (%)					
CD25+CD127low/- Tregs	2.6 ± 2.3	0.2 – 12.7	1.5 ± 1.1	0.4 – 4.9	0.01**
CD25low/-CD127+	68.0 ± 13.6	29.1 – 89.6	77.4 ± 9.8	44.7 – 86.5	0.00**
CD25-CD127-	19.4 ± 11.8	2.8 – 56.7	10.4 – 8.6	3.1 – 36.9	0.00**
$CD25^+127^{low/-}$ Tregs - FoxP3 Expression Level					
FoxP3 (%)	29.0 ± 21.4	1.5 – 72.9	25.7 ± 13.4	2.4 – 49.2	0.79**
FoxP3 (MFI)	300.4 ± 65.1	210 – 535	300.2 ± 113.3	207 – 764	0.30**
$CD19^+$ B cell subsets (%)					
$CD38^{hi}CD24^{hi}$ Bregs	10.1 ± 3.8	2.7 – 23.5	9.0 ± 2.4	5.4 – 14.6	0.22*
$CD38^{hi}CD24^-$ Plasmablast	2.4 ± 3.1	0.1 – 14.1	2.1 ± 2.1	0 – 8.4	0.96**
$CD38^{int}CD24^{int}$ Mature Naive B Cell	58.7 ± 8.6	39.1 – 77.1	55.0 ± 9.8	38.1 – 73.6	0.13*
$CD38^-CD24^+$ Primarily Memory B Cell	14.2 ± 5.6	5.7 – 26.0	18.9 ± 5.3	11.1 – 30.1	0.00*
$CD38^-CD24^-$ New Memory B Cell	4.9 ± 3.6	0.1 – 21.1	6.4 ± 3.2	2.4 – 12.3	0.06**

Treg: Regulatory T cells, Bregs: Regulatory B cells, * Independent sample t-test, **Mann–Whitney U test

with THI compared to the control group (p = 0.04, p = 0.05, respectively). In the analysis of $CD4^+$ Th cell subsets according to CD25 and CD127 expressions, the $CD4^+CD25^{low/-}CD127^+$ Th cells decreased (p = 0.00), while the $CD4^+CD25^-CD127^-$ Th cells and the $CD4^+CD25^+CD127^{-/low}$ Tregs increased in the THI group (p = 0.00, p = 0.01) (Table III) (Fig. 1).

Flow cytometric analysis of B cells showed that the $CD38^-CD24^+$ primarily memory B cells were reduced in the THI group (p = 0.00). There was no significant difference in the $CD38^{hi}CD24^{hi}$ Bregs, the $CD38^{int}CD24^{int}$ mature naive B cell, the $CD38^{bri}CD24^-$ plasmablast cells, and $CD38^-CD24^-$ new memory B cell subset (p > 0.05) (Table III) (Fig. 3).

Correlation analysis showed that there was no relationship between Tregs/Bregs and serum IgG, IgA, and IgM levels; frequency of infection; and intravenous IgG requirement. However, the ratio of FoxP3 in Tregs was negatively correlated with IgG recovery age.

Discussion

In this study, to elucidate the pathophysiology of THI, we analyzed, for the first time, Th subsets in regards to CD127 and CD25 expressions and B cell subsets according to CD38 and CD24 expressions in 40 children with THI. This study demonstrated that patients with THI had some changes in the Th subsets, including $CD4^+CD25^+CD127^{-/low}$ Tregs and B cell subsets. While the percentage of CD127 of $CD3^+$ T and $CD3^+CD4^+$ Th cells decreased in children with THI, CD127 expression (MFI) increased. The children with THI had higher $CD4^+CD25^+CD127^{low/-}$ Tregs than the controls, but their $CD19^+CD38^-CD24^+$ primarily memory B cells were low.

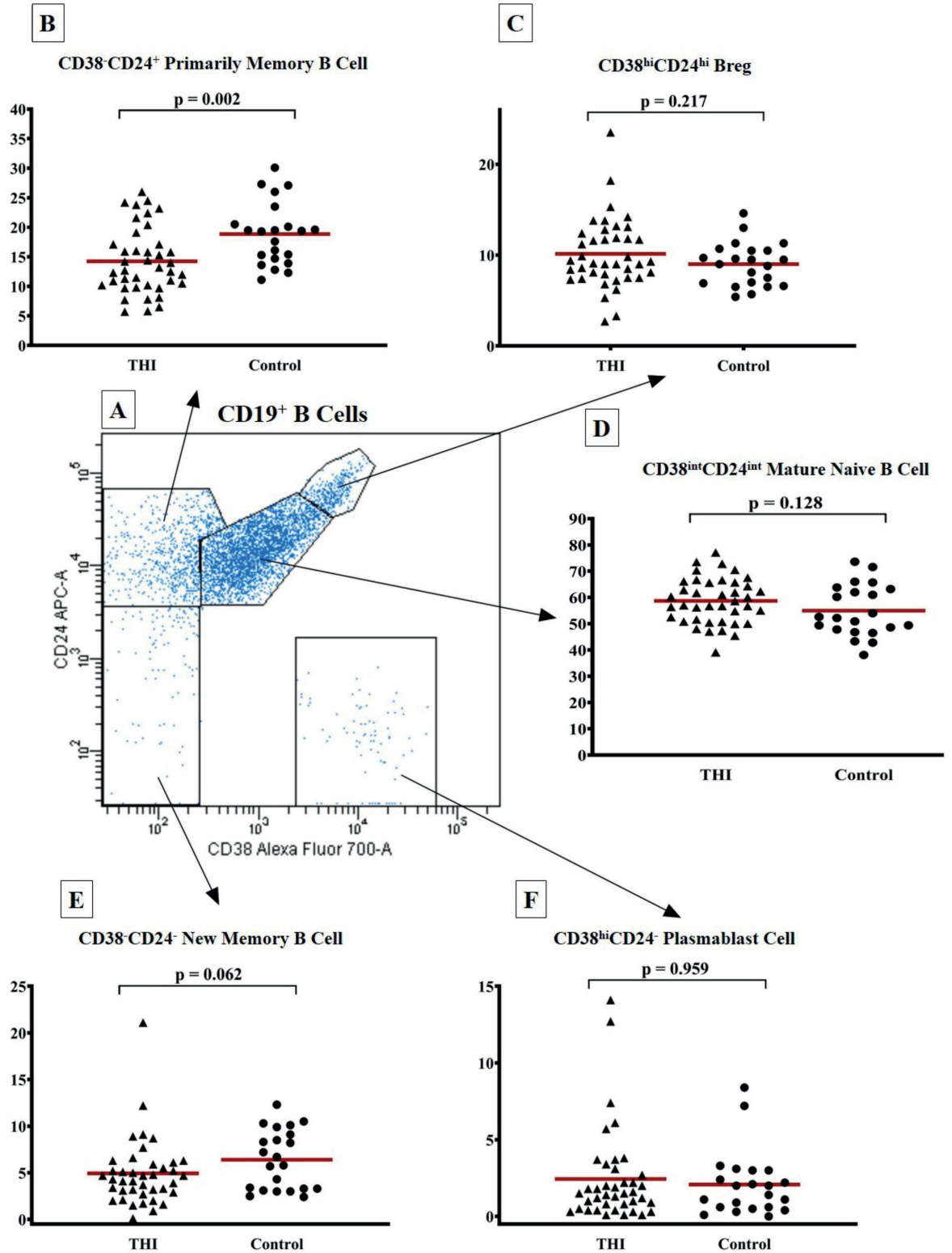

Fig. 3. Flow cytometric gating strategy of B cell subsets (A) in patients with THI and control groups (B-F). $CD19^+$ B cells were classified as $CD38^-CD24^+$ primarily memory B cell (B), $CD38^{hi}CD24^{hi}$ Bregs (C), $CD38^{int}CD24^{int}$ mature naive B cell (D), $CD38^-CD24^-$ new memory B cell (E), $CD38^{hi}CD24^-$plasmablast (F).

In our study, $CD4^+CD25^+CD127^{-/low}$ Tregs were found to increase in children with THI. $CD4^+CD25^+FoxP3^+$ Tregs in THI were first studied by Rutkowska et al.[11-13], and they reported elevated Treg numbers in children with THI[11], which is consistent with our findings. We found no significant difference in FoxP3 expression of Tregs in patients with THI compared to the control. However, the FoxP3 ratio of Tregs was negatively correlated with the IgG recovery age in THI.

Siegel et al.[6] reported that antibody production deficiency might be related to immature or delayed development of Th cells. In the current study, we found the Th cell count to be normal. However, IL-7 receptor-α (CD127) expression of total T and Th cells was reduced. In our study, the low percentage of CD127 in T cells may be expected to affect cellular immunity. However, the increased expression of CD127 (MFI) in T cells may be compensating for developmental and functional defects in these cells.

Dunham et al.[15], in their study of patients with AIDS, found that the $CD25^{low/-}CD127^+$ subset significantly decreased and the $CD25^-CD127^-$ subset increased in HIV–infected adult patients. A study by Shen et al.[32] among chronic patients with human hepatitis C virus (HCV) reported that all three Th cell subsets ($CD25^+CD127^{low/-}$, $CD25^{low/-}CD127^+$, and $CD25^-CD127^-$) increased compared to the healthy controls. In both studies among patients with HIV and HCV, the change in $CD4^+$ T cell subsets defined according to CD127 and CD25 expression profiles may be associated with mitigating chronic immune activation. Rutkowska et al.[12] reported that patients with THI had low serum IL-2 levels. These findings indicated that variations in different fractions of $CD4^+$ T cells and low efficiency of the immune response might be associated with infection susceptibility in children with THI.

In this study, Bregs and other B cell subsets according to CD38 and CD24 expressions were first investigated in THI. Primarily memory B cells significantly decreased in the THI group compared to the control. However, there was no significant difference in the percentage of Bregs, plasmablast, mature naive B cell, and new memory B cell subsets between the groups. In Eroglu et al.[28], memory B cell subsets were low in patients with THI, but there was no significant difference. Our previous study determined low immunoglobulin class switching and IgM^+ memory B cells, and the percentage of CD21 and CD81 that constituted the CD19 complex increased in THI.[10] In this study, CD38 expression in $CD19^+$ B cells was also low in children with THI. CD38 controls a signaling pathway involved in the growth, survival, and activation of lymphoid cells.[33,34] Deaglio et al.[35] reported that CD38-mediated signals are regulated at three distinct levels, and the CD19/CD81 complex mediates one of them. In vivo and ex vivo stimulation studies have revealed that B cells without CD81 have a hyperactive phenotype, and therefore, CD81 negatively regulates B cell activation.[35] The increased number of CD81 may suppress CD38 expression and cause insufficient B cell activation due to developed hypogammaglobulinemia in THI.

In our series, IgG levels reached normal levels at 24–58 months. Although the upper cutting age of normal IgG production is reported as 3–4 years, some studies indicate delayed recovery of IgG levels extending to 10 years.[3] Most children with THI spontaneously recover their IgG levels, which is consistent with our findings.[36,37] These studies showed that if these patients with THI were not suffering from recurrent or severe infections during their follow-up, IgG levels achieved normal levels within the expected time.[36,37]

Our study demonstrated that changes in the T cell compartment, including a decreased percentage of CD127 and increased CD127 expression in T cells, may be related to immune compensation mechanisms in THI. The higher percentage of $CD4^+CD25^+CD127^{-/low}$ Tregs and lower primary memory B cells may cause a delay in antibody production in children with THI. To summarize, our observations about changes in the T cell and B cell subsets may

contribute to improving our understanding of the pathogenesis of THI. Further studies are needed to determine whether the changes in the T cell compartment are associated with chronic immune activation caused by recurrent viral and bacterial stimulation.

Ethical approval

This study was approved by the Ethical Committee of Selcuk University Medical Faculty (2015/265).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: HA, AE; data collection: AE, HU, TG; analysis and interpretation of results: HA, AE; draft manuscript preparation: HA, AE, TG. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

This work was supported by the Scientific Research Projects Committee of Selcuk University (16401133).

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Walker AM, Kemp AS, Hill DJ, Shelton MJ. Features of transient hypogammaglobulinaemia in infants screened for immunological abnormalities. Arch Dis Child 1994; 70: 183-186. https://doi.org/10.1136/adc.70.3.183
2. Ballow M. Primary immunodeficiency disorders: antibody deficiency. J Allergy Clin Immunol 2002; 109: 581-591. https://doi.org/10.1067/mai.2002.122466
3. Dalal I, Reid B, Nisbet-Brown E, Roifman CM. The outcome of patients with hypogammaglobulinemia in infancy and early childhood. J Pediatr 1998; 133: 144-146. https://doi.org/10.1016/S0022-3476(98)70195-7
4. Yorulmaz A, Artaç H, Reisli I. Evaluation of patient follow-up with transient hypogammaglobulinemia in infancy diagnosis. J Contemp Med 2019; 9: 15-20. https://doi.org/10.16899/gopctd.534014
5. Kilic SS, Ozel M, Hafizoglu D, Karaca NE, Aksu G, Kutukculer N. The prevalences [correction] and patient characteristics of primary immunodeficiency diseases in turkey--two centers study. J Clin Immunol 2013; 33: 74-83. https://doi.org/10.1007/s10875-012-9763-3
6. Siegel RL, Issekutz T, Schwaber J, Rosen FS, Geha RS. Deficiency of T helper cells in transient hypogammaglobulinemia of infancy. N Engl J Med 1981; 305: 1307-1313. https://doi.org/10.1056/NEJM198111263052202
7. Ochs HD, Stiehm ER, Winkelstein JA. Antibody deficiencies. In: Ochs HD, Stiehm ER, Winkelstein JA (eds). Immunologic disorders in infants & children (5th ed). Philadelphia: Elsevier Saunders, 2004: 357-373.
8. McGeady SJ. Transient hypogammaglobulinemia of infancy. In: Sullivan KE, Stiehm ER (eds). Stiehm's Immune Deficiencies (1st ed). Amsterdam: Academic Press, 2014: 417-426. https://doi.org/10.1016/B978-0-12-405546-9.00018-2
9. Kowalczyk D, Baran J, Webster AD, Zembala M. Intracellular cytokine production by Th1/Th2 lymphocytes and monocytes of children with symptomatic transient hypogammaglobulinaemia of infancy (THI) and selective IgA deficiency (SIgAD). Clin Exp Immunol 2002; 127: 507-512. https://doi.org/10.1046/j.1365-2249.2002.01701.x
10. Artac H, Kara R, Gokturk B, Reisli I. Reduced CD19 expression and decreased memory B cell numbers in transient hypogammaglobulinemia of infancy. Clin Exp Med 2013; 13: 257-263. https://doi.org/10.1007/s10238-012-0200-y
11. Rutkowska M, Lenart M, Bukowska-Strakovà K, et al. The number of circulating CD4+ CD25high FoxP3+ T lymphocytes is transiently elevated in the early childhood of transient hypogammaglobulinemia of infancy patients. Clin Immunol 2011; 140: 307-310. https://doi.org/10.1016/j.clim.2011.04.003
12. Rutkowska M, Trzyna E, Lenart M, et al. The elevated number of circulating regulatory T cells in patients with transient hypogammaglobulinemia of infancy is not associated with any abnormalities in the genes encoding the TGF-β receptors. Clin Immunol 2013; 149: 83-85. https://doi.org/10.1016/j.clim.2013.06.008
13. Siemińska I, Rutkowska-Zapała M, Bukowska-Strakova K, et al. The level of myeloid-derived suppressor cells positively correlates with regulatory T cells in the blood of children with transient hypogammaglobulinaemia of infancy. Cent Eur J Immunol 2018; 43: 413-420. https://doi.org/10.5114/ceji.2018.81359

14. Fry TJ, Mackall CL. The many faces of IL-7: From lymphopoiesis to peripheral T cell maintenance. J Immunol 2005; 174: 6571-6576. https://doi.org/10.4049/jimmunol.174.11.6571

15. Dunham RM, Cervasi B, Brenchley JM, et al. CD127 and CD25 expression defines CD4+ T cell subsets that are differentially depleted during HIV infection. J Immunol 2008; 180: 5582-5592. https://doi.org/10.4049/jimmunol.180.8.5582

16. Liu W, Putnam AL, Xu-Yu Z, et al. CD127 expression inversely correlates with FoxP3 and suppressive function of human CD4+ T reg cells. J Exp Med 2006; 203: 1701-1711. https://doi.org/10.1084/jem.20060772

17. Buffa S, Pellicanò M, Bulati M, et al. A novel B cell population revealed by a CD38/CD24 gating strategy: CD38(-)CD24(-) B cells in centenarian offspring and elderly people. Age (Dordr) 2013; 35: 2009-2024. https://doi.org/10.1007/s11357-012-9488-5

18. Funaro A, Morra M, Calosso L, Zini MG, Ausiello CM, Malavasi F. Role of the human CD38 molecule in B cell activation and proliferation. Tissue Antigens 1997; 49: 7-15. https://doi.org/10.1111/j.1399-0039.1997.tb02703.x

19. Kay R, Rosten PM, Humphries RK. CD24, a signal transducer modulating B cell activation responses, is a very short peptide with a glycosyl phosphatidylinositol membrane anchor. J Immunol 1991; 147: 1412-1416.

20. Suzuki T, Kiyokawa N, Taguchi T, Sekino T, Katagiri YU, Fujimoto J. CD24 induces apoptosis in human B cells via the glycolipid-enriched membrane domains/rafts-mediated signaling system. J Immunol 2001; 166: 5567-5577. https://doi.org/10.4049/jimmunol.166.9.5567

21. Rosser EC, Mauri C. Regulatory B cells: Origin, phenotype, and function. Immunity 2015; 42: 607-612. https://doi.org/10.1016/j.immuni.2015.04.005

22. Mauri C, Bosma A. Immune regulatory function of B cells. Annu Rev Immunol 2012; 30: 221-241. https://doi.org/10.1146/annurev-immunol-020711-074934

23. van de Veen W, Stanic B, Wirz OF, Jansen K, Globinska A, Akdis M. Role of regulatory B cells in immune tolerance to allergens and beyond. J Allergy Clin Immunol 2016; 138: 654-665. https://doi.org/10.1016/j.jaci.2016.07.006

24. Jeske SS, Brand M, Ziebart A, et al. Adenosine-producing regulatory B cells in head and neck cancer. Cancer Immunol Immunother 2020; 69: 1205-1216. https://doi.org/10.1007/s00262-020-02535-6

25. Yesillik S, Agrawal S, Gollapudi SV, Gupta S. Phenotypic analysis of CD4+ Treg, CD8+ Treg, and Breg cells in adult common variable immunodeficiency patients. Int Arch Allergy Immunol 2019; 180: 150-158. https://doi.org/10.1159/000501457

26. Vlkova M, Ticha O, Nechvatalova J, et al. Regulatory B cells in cvid patients fail to suppress multifunctional IFN-γ+ TNF-α+ CD4+ T cells differentiation. Clin Immunol 2015; 160: 292-300. https://doi.org/10.1016/j.clim.2015.06.013

27. Bayram RO, Özdemir H, Emsen A, Türk Dağı H, Artaç H. Reference ranges for serum immunoglobulin (IgG, IgA, and IgM) and IgG subclass levels in healthy children. Turk J Med Sci 2019; 49: 497-505. https://doi.org/10.3906/sag-1807-282

28. Eroglu FK, Aerts Kaya F, Cagdas D, et al. B lymphocyte subsets and outcomes in patients with an initial diagnosis of transient hypogammaglobulinemia of infancy. Scand J Immunol 2018; 88: e12709. https://doi.org/10.1111/sji.12709

29. Oleinika K, Mauri C, Salama AD. Effector and regulatory B cells in immune-mediated kidney disease. Nat Rev Nephrol 2019; 15: 11-26. https://doi.org/10.1038/s41581-018-0074-7

30. Ucaryilmaz H, Koksal H, Emsen A, Kadoglou N, Dixon JM, Artac H. The role of regulatory T and B cells in the etiopathogenesis of idiopathic granulomatous mastitis. Immunol Invest 2022; 51: 357-367. https://doi.org/10.1080/08820139.2020.1832114

31. Ikincioğullari A, Kendirli T, Doğu F, et al. Peripheral blood lymphocyte subsets in healthy Turkish children. Turk J Pediatr 2004; 46: 125-130.

32. Shen T, Chen X, Xu Q, Lu F, Liu S. Distributional characteristics of CD25 and CD127 on CD4+ T cell subsets in chronic HCV infection. Arch Virol 2010; 155: 627-634. https://doi.org/10.1007/s00705-010-0626-z

33. Campana D, Suzuki T, Todisco E, Kitanaka A. CD38 in Hematopoiesis. In: Mehta K, Malavasi F (eds). Human CD38 and related molecules. Chem immunol. Basel: Karger, 2000: 169-188. https://doi.org/10.1159/000058768

34. Mallone R, Funaro A, Zubiaur M, et al. Signaling through CD38 induces NK cell activation. Int Immunol 2001; 13: 397-409. https://doi.org/10.1093/intimm/13.4.397

35. Deaglio S, Vaisitti T, Billington R, et al. CD38/CD19: A lipid raft-dependent signaling complex in human B cells. Blood 2007; 109: 5390-5398. https://doi.org/10.1182/blood-2006-12-061812

36. Keles S, Artac H, Kara R, Gokturk B, Ozen A, Reisli I. Transient hypogammaglobulinemia and unclassified hypogammaglobulinemia: 'Similarities and differences'. Pediatr Allergy Immunol 2010; 21: 843-851. https://doi.org/10.1111/j.1399-3038.2010.01010.x

37. Ozen A, Baris S, Karakoc-Aydiner E, Ozdemir C, Bahceciler NN, Barlan IB. Outcome of hypogammaglobulinemia in children: Immunoglobulin levels as predictors. Clin Immunol 2010; 137: 374-383. https://doi.org/10.1016/j.clim.2010.08.010