T Cell Abnormalities in Common Variable Immunodeficiency

Gholamreza Azizi[1,2,3], Nima Rezaei[2,4,5], Fatemeh Kiaee[2,3], Naiimeh Tavakolinia[2,3], Reza Yazdani[6], Abbas Mirshafiey[7], Asghar Aghamohammadi[2,3]*

1. Department of Laboratory Medicine, Imam Hassan Mojtaba Hospital, Alborz University of Medical Sciences, Karaj, Iran

2. Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

3. Primary Immunodeficiency Diseases Network (PIDNet), Universal Scientific Education and Research Network (USERN), Tehran, Iran

4. Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

5. Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

6. Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

7. Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

***Correspondence to:** Prof. Asghar Aghamohammadi, Children's Medical Center Hospital, 62 Qarib St., Keshavarz Blvd., Tehran 14194, Iran, Tel: + 98 21 6642 8998, Fax: + 98 21 66923054, E-mail: aghamohammadi@sina.tums.ac.ir

Short title: T cell abnormalities in CVID

Conflicts of interest and financial sources:

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

doi: 10.18176/jiaci.0069

Abstract

Common variable immunodeficiency (CVID) is the most common clinical primary immunodeficiency, which characterized by defect in B cells differentiation to plasma and memory B cells. Moreover, numerous T cell abnormalities have been described in these patients such as, decreased T cell count and proliferative response, increased of T cell activation and apoptosis, and abnormalities in cytokine production. The aim of this review is to describe phenotypic and functional defects of T cells in CVID patients, and to review the literature with respect to the effects of immunoglobulin substitution on the T cell component of CVID patients.

Key words: Common variable immunodeficiency, T cell, T helper cell, Regulatory T cells

Resumen

La inmunodeficiencia común variable (CVID) es la inmunodeficiencia primaria más frecuente. Se caracteriza por un defecto en la diferenciación de linfocitos B hacia células plasmáticas y linfocitos B memoria. Se han descrito numerosas alteraciones en los linfocitos T de estos pacientes, tales como disminución en el número de linfocitos T y en sus respuestas proliferativas, aumento en la activación de células T y en la apoptosis, así como alteraciones en la producción de citokinas. El objetivo de esta revisión es describir las alteraciones funcionales y fenotípicas de los linfocitos T en los pacientes con CVID y revisar la bibliografía en relación a los efectos que la administración de inmunoglobulinas produce en los linfocitos T de los pacientes con CVID.

Palabras clave:

Inmunodeficiencia común variable; células T; células T helper; células T reguladoras.

doi: 10.18176/jiaci.0069

1. Introduction

Common variable immunodeficiency (CVID) is the most common clinical primary immunodeficiency (PID), which defined by defects in B-cell differentiation into plasma and memory B cells [1, 2]. The affected patients are characterized by increased susceptibility to recurrent infection, because of low levels of immunoglobulin in serum as well as reduced specific antibody response to protein and polysaccharide antigens [3-6]. Patients may also have a wide variety of clinical complications, including autoimmunity and inflammatory condition, lymphoid malignancy, granuloma and enteropathy, which have been recently considered in classification of CVID into clinical phenotypes with variable prognosis [7-11].

The most important cellular alteration in CVID patients is severe B cell defect, which leads to hypogammaglobulinemia. However, alteration in frequency and function of T cells has also been demonstrated in a number of patients with CVID [12-14]. The influence of these defects on the interaction between T and B cells could explain not only the defective antibody production, but also the development of other complications, including recurrent bacterial and viral infections, gastrointestinal disease, lymphoma, autoimmune, inflammatory features and early-onset bronchiectasis in CVID patients [15-17]. In this review, our aim is to describe phenotypic and functional defects of T cells in CVID patients, and to review the literatures with respect to the effects of immunoglobulin intravenous (IGIV) infusion on the T cell components in CVID.

2. T-cell abnormalities in CVID

There are various T cell subsets that all perform different functions, but among them the most important are $CD4^+$ and $CD8^+$ T cells (**Table 1**). Recent researches demonstrated that a subgroup of patients with clinically diagnosed CVID is T-cell deficient. However, based on revised European Society for Immunodeficiencies (ESID) diagnostic criteria for CVID (2014), there should be no evidence of profound T-cell deficiency. The profound T-cell deficiency in CVID patients are defined as two out of the following: 1- $CD4^+$ cell numbers/μL: 2–6 y <300, 6–12 y <250, >12 y <200; 2- percent of naive $CD4^+$ T cells: 2–6 y <25%, 6–16 y <20%, >16 y <10%; and 3- T-cell proliferation absent [18]. Those CVID patients who undergo profound T-cell deficiency will need to be considered as combined immunodeficiency (CID) [19, 20].

doi: 10.18176/jiaci.0069

Traditionally the reported T-cell abnormalities in CVID are including a reduced T cell count and decreased lymphocyte proliferation in response to mitogens and antigens, defective T-cell signaling, decline of regulatory T cells (Tregs), uncontrolled T cell polarization, elevated levels of T-cell activation markers and abnormality in cytokine production secondary to the gene polymorphisms [12-14, 21-26].

CVID patients with T-cell abnormalities manifested a severe phenotype which presented more often with gastrointestinal tract disease, splenomegaly, granuloma and lymphoma [27, 28]. Moreover, parental consanguinity in CVID patients (cCVID) is associated with the severe T-cell abnormalities, lower age at onset and diagnosis, severity of disease and higher mortality rate. It is demonstrated that in cCVID patients naive $CD4^+$ T cells are decreased, while activated $CD4^+$, $CD95^+$, $CD8^+$ and HLA-DR^+ T cells are increased, compared to patients without parental consanguinity. In these patients splenomegaly, granulomatous disease, polyclonal lymphocytic infiltration, bronchiectasis, enteropathy and opportunistic infections were more frequent [27, 29-31].

Recently, T-cell receptor excision circles (TRECs) and kappa-deleting recombination excision circles (KRECs) as circular DNA segments that persist in the T cells and B cells, are considered markers of new lymphocyte output [32]. Kamae et al. (2013) indicated that low TREC and/or KREC levels are useful biomarkers that associated with the overall survival rate in CVID patients [33]. Moreover, TRECs and KRECs are positively correlated to absolute counts of naive T and naive B, as well as to memory B cells, respectively. Accordingly, low TRECs and KRECs values reflect low naive T and B cells in some CVID patients with the potential to develop the CID phenotype [34]. In conclusion, TREC and KREC are valuable biomarkers for assessment of clinical severity, pathogenesis and prognosis of CVID patients in addition to distinguish between CVID and CID.

3. $CD4^+$ T cells defects in CVID

Phenotypic and functional defects of $CD4^+$ T cells in CVID patients have been known for a decade [35-37]. These abnormality are including increased number of activated $CD4^+$ T cells and reduced number of total, naive and memory $CD4^+$ T cells (**Table 2**), along with functional impairment such as reduced proliferation capacity and failure in cytokine production [37, 38]. This reduction in $CD4^+$ T cells is associates with decrease in thymic output, increase in T-cell turnover and spontaneous apoptosis [12].

doi: 10.18176/jiaci.0069

3.1. Naive CD4$^+$ T cell: As mentioned, CVID patients have reduced number of naive CD4$^+$ T cells and RTE cells. In a study by Oraei et al. (2012), CVID patients have lower number of naive and RTE CD4$^+$ T cells in comparison with healthy controls. Interestingly, they showed that this reduction in male were more apparent than female patients [35]. Meanwhile, reduction in both total CD4$^+$ and RTE counts of T cells, most pronounced in those CVID patients whom are involved with autoimmune cytopenia or polyclonal lymphoproliferation [13, 39]. Several studies shown that the severity and prognosis of CVID is reflected in a parallel loss of naive CD4$^+$ T cells and there are a strong correlation between naive CD4$^+$ T cell counts and clinical features [12, 13, 39, 40]. In this regard, when CVID patients were classified on the basis of clinical phenotypes (infection only, polyclonal lymphoproliferation, cytopenias, organ-specific autoimmunity, lymphoid malignancy and enteropathy), the autoimmune cytopenia and organ-specific autoimmunity groups had the most significantly reduced number of naive CD4$^+$ T cells, followed by the polyclonal lymphoproliferation group [13]. Therefore, a new classification system according to the number of naive CD4$^+$ T cells has been proposed and CVID patients were divided into three separate groups. Group A has significant decreased numbers of CD4$^+$ naive T cells along with massive T-cell activation. Other characteristics including elevated apoptosis, disruption of normal TCR repertoires, splenomegaly and clinically more severe immunodeficiency are also attributed to this group. In group B, these mentioned features for group A were also present but they were less pronounced. Group C had normal numbers of naive CD4$^+$ T cells, but an alteration in the CD8$^+$ T cell compartment was presented. In addition, in group C, splenomegaly was less common than in the other groups and was correlated with a milder clinical future [12, 41, 42].

3.2. Activated CD4$^+$ T cell: Elevation in CD4$^+$ T cell count and its activation markers are also demonstrated in CVID patients [43]. These abnormalities are including an increase in HLA-DR, CD29, CD45RO, CD95 (APO-1/Fas) and a decrease in CD27, CD45RA and CD62L, especially in patients with increased number of CD21low B cells and decreased number of memory and regulatory B cells [25, 44]. CVID patients present with both low numbers of regulatory B cells and increased numbers of IFN-γ^+TNF-α^+CD4$^+$ T cells [44, 45]. The defect in regulatory B cell responses, to T cell stimulation and differentiation explains the excessive CD4$^+$ T cells activation that is a frequent finding in CVID patients.

doi: 10.18176/jiaci.0069

In a study by Carbone et al. (2006), higher frequency of activated $CD4^+$ T cells in patients with suspected IgG hyper catabolism was reported, as well as in those patients with clinical complications including lymphoid proliferation, splenomegaly and autoimmune disease [43]. Another study showed that CVID patients with autoimmune cytopenia have increased number of activated $CD4^+$ T cells, decrease numbers of naive T cell along with an increased proportion of CD21 low B cells [15]. However, Boileau et al. (2011) proposed that this concurrent T and B cells phenotypic picture cannot be seen in CVID patients with other autoimmune manifestations and/or patients with splenomegaly [15, 46]. Overall, according to recent findings on correlation of CD21 low B cells in CVID and autoimmunity such as autoimmune cytopenia and rheumatoid arthritis (RA) [15, 46], it is suggested that in order to break down the B cell tolerance against auto-antigens, restricted subset of B cell and help from activated $CD4^+$ T cells are needed. On the other hand it is demonstrated that dysfunctional BLK in B-cells of CVID patients perturbs proliferation and ability of B cells to elicit antigen-specific $CD4^+$ T-cell responses [47]. These findings prove that T and B cell abnormalities in CVID are partially related to each other.

3.3. Memory $CD4^+$ T cells: CVID patients also have defects in memory $CD4^+$ T cells; however, literatures review showed a few key studies in this field. In a study, Giovannetti et al. (2007) showed that absolute counts of central memory $CD4^+$ T cells have decrease in CVID patients, whereas no significant differences were detected for the effector memory cells [12]. In another study Bateman et al. (2012) revealed that within $CD4^+$ memory subpopulations both central and effector memory cells had a significant difference between CVID clinical groups. They report $CD4^+$ central memory T cells were reduced in the patients of autoimmune cytopenias group compared to both healthy and disease controls [13]. Regarding, memory T cells has different capacities to proliferate in response to antigen and/or cytokines to perform effectors functions, therefore recurrent infections and poor response to vaccine in CVID patients maybe a result of long-term defective immunity which is not caused by memory T cells.

4. T helper cells defects

There is little literature available that investigates T helper subsets and their pathogenic relationship with CVID. Barbosa et al. (2011) for the first time reported a

doi: 10.18176/jiaci.0069

decline in the frequency of circulating Th17 cells in CVID patients. In this study no association was demonstrated between the frequency of Th17 cells and transitional B cells. In contrast, they showed a negative correlation between Th17 cells and expansion of activated non-differentiated CD21 low B cells. Therefore, decline in the frequency of circulating Th17 cells are matched by the B-cell disturbances, a representative feature of germinal centers disruption [48]. Moreover, the frequency of Th17 cells was found to negatively correlate with activated $CD4^+$ T cell in patients with CVID, while there was no correlation with naive and memory T cell balances. The frequency of Th1 cells was found to negatively correlate with naive $CD4^+$ T cells and positively with the levels of activated $CD4^+$ T cell in CVID patients [48]. In another study Ganjalikhani-Hakemi et al. (2014) evaluated the Th17 cell specific genes expression in CVID patients. Their result showed that frequencies of Th17 cells in the CVID patients were markedly decreased compared with the healthy individuals. Moreover, the mRNA levels of IL-17 and RORC2 in these patients was strongly lower than healthy controls, but slight reduction in the IL-23R expression has seen in the CVID patients [49]. As IL-17 and possibly Th17 cells can contribute to germinal centers function [50], these findings are consistent with the results of Barbosa et al. which propose the levels of IL-17 and Th17 cells were presenting a negative correlation with the pathological expansion of a B cell population associated with impaired germinal centers function in CVID [48]. In addition, IL-17 is also produced by follicular helper $CD4^+$ T cells. According to the study by Romberg et al. (2014), the circulating follicular helper $CD4^+$ T cells were significantly diminished in the CVID patients compared with the healthy subjects [51]. Therefore, the reduction of IL-17 in the CVID patients, in addition to Th17 defects, may be attributable to their diminished follicular helper T cells population.

Several studies demonstrated that Th17 cells and their proportion increased in a variety of autoimmune diseases such as autoimmune hemolytic anemia and immune thrombocytopenia [52], RA [53], psoriasis [54], and lupus [55]. However, Barbosa et al. found no increase in the frequency of Th17 cells in CVID patients with autoimmune manifestations, even when CVID patients were subdivided based on the type of autoimmune disorders including organ specific autoimmunity and autoimmune cytopenias. In contrast, the CD21 low B cell subset was significantly increased in those CVID patients who have autoimmunity [15, 48]. In conclusion, no

doi: 10.18176/jiaci.0069

obvious association between autoimmune manifestations and frequency of Th17 cells and its pro-inflammatory cytokines was observed in CVID patients. However, in recent study, there were some findings about Th1/Th2 balance in CVID patients. Th1 cells seem to be more involved in the disease pathogenesis than Th2 cells. Those CVID patients with hepatomegaly had higher IL-2 and IFN-γ on stimulated $CD4^+$ T cells, and patients with granuloma were found to have higher CCR5 expression on $CD4^+$ T cells suggesting that Th1 cells may play a role in granuloma formation in CVID patients [14]. Overall, increased production of some chemokines [56] and cytokines, including IFN-γ [57], TNF-α [12], IL-12 [57], IL-9 [49], IL-4 and IL-10 [58] by Th subsets have been reported in in CVID patients [59]; some of these cytokines play a pivotal role in antibody synthesis. Rezaei et al. (2008) investigated Th1 and Th2 cytokine levels in serum of CVID patients. The results showed that the levels of IL-4 and IL-10 as Th2 cytokines were significantly higher in the CVID patients. However, there were no significant differences in Th1 cytokines (IL-2 and IFN-γ) compared to healthy controls [58]. Paradoxically, in a report by Del Vecchio et al. (2008), there is not seen any difference in IL-4 production by peripheral $CD4^+$ T cells but reduced IL-5 productions (a cytokine involved in the late regulation of B cell differentiation into plasma cells) was observed by these cells. Although the sample size of this study was low and only four CVID patients were evaluated, they concluded that the reduction of IL-5 may contribute to the defective antibody production in CVID patients [60]. The presented data regarding the altered cytokine signature in CVID patients are contradictory. We proposed that these altered cytokine profile may be attributed to the different type of specimen (serum, PBMCs or purified $CD4^+$ T cells), evaluation of cytokine secretion or its gene expression, different sample size in studies, patients clinical status and associated complications, as well as myeloid and lymphoid lineages activation which possibly driven by the high prevalence of bacterial infections in the gastrointestinal or respiratory tracts in some of CVID patients.

5. Regulatory T cell defects

Treg cells are key regulators of immune responses and play a crucial role in limiting unwanted and persistent immune activation. Several studies demonstrated that Tregs are reduced in CVID patients [61-63]. Moreover, residual Tregs appear to have

doi: 10.18176/jiaci.0069

reduced suppressive capacity [36] with down-regulation of FoxP3 protein and diminished expression of inhibitory markers such as CTLA-4 and GITR [64]. In contrast, recently Kutukculer et al. (2015) proposed Tregs do not play an important role in the pathogenesis of CVID. They reported not only percentages, but also absolute counts of Treg cells did not show any significant difference between CVID patients and healthy controls and also between severe and moderate disease patients [14].

Totally, there is a significant correlations between low numbers of Treg cells and autoimmune manifestations [61, 63, 65, 66] as well as granulomatous lesion [65] and splenomegaly [61]. Firstly, Genre et al. (2009) reported that CVID patients with autoimmune future had a significantly reduced frequency of Treg cells accompanied by a decreased intensity of Foxp3 expression. Moreover, the expression levels of Foxp3 in CVID patients without autoimmunity did not differ from those in healthy subjects [66]. Arumugakani et al. (2010) revealed low frequency of Treg cells is correlated with expansion of CD21low B cells in CVID patients with autoimmunity, while patients with splenomegaly have significant reduction in frequency and number of Treg cells [61]. In similar study Arandi et al. (2013) showed that CVID patients with autoimmunity have noticeably reduced proportion of Treg cells compared to those CVID patients without autoimmune complications [64]. As can be seen, the majority of the studies cited relies on phenotypic analysis of Treg cells in peripheral blood and have less focus on the study of Treg cell functions. Yu et al. [63] showed that sorted Tregs from CVID patients with autoimmune disease are compromised in their suppressive activity and has reduced ability to suppress proliferation of autologous and allogenic effector $CD4^+$ T cells, compared with CVID patients without autoimmunity. Furthermore, the down regulation of FoxP3, granzyme A and pStat5 was significantly correlated with the degree of Treg cell dysfunction in CVID [63]. In another study in our research center, Arandi et al. (2013), using Tregs suppression assay proved that suppressive functions of Tregs were impaired. Moreover, IL-10 was produced at markedly lower amounts by Tregs in CVID patients. No difference was seen in TGF-β concentration between patients and the control group [36]. Moreover, in two other studies by Holm et al. (2003) and Zhou et al. (1998) the authors reported a decreased level of IL-10 in CVID [66, 67]. Regarding abnormality of Treg cells in CVID patients, it could be concluded that cellular dysregulations including elevation in activated $CD4^+$ T cell count especially in those

doi: 10.18176/jiaci.0069

with autoimmune manifestation may be a consequence of lower number and reduced suppressive capacity of Tregs.

6. CD8 T cell defects in CVID

Like $CD4^+$ T cells, $CD8^+$ T cells also have defect in CVID patients. It is revealed that naive and effector memory $CD8^+$ T cells are reduced in CVID patients [13], while activated $CD8^+$ T cell are increased [43, 68]. Bateman et al. (2012) reported that the reduction in naive $CD8^+$ T cells count was most significant in those CVID patients with autoimmune cytopenia [13].

A high expansion of activated $CD8^+$ T-cells has also been reported in CVID patients [68, 69]. It is demonstrated that $CD8^+$HLA-DR^+, $CD8^+CD38^+$ and $CD8^+CD38^+$HLA-DR^+ T-cells are expanded in CVID patients [43], and this is restricted to patients with clinical complications [70], including autoimmunity, splenomegaly, lymphoid proliferation and granulomatous disease. Moreover, CVID patients with activated $CD8^+$ T-cells showed a reduction of their TCR repertoire diversity which was more severe in those CVID patients with above mentioned complications [69]. In addition to the HLA-DR, $CD8^+$T cells of CVID patients with autoimmunity have higher expression levels of granzyme B [68]. Moreover, $CD8^+$HLA-DR^+ T cells are increased in CVID patients with impaired memory B-cell differentiation. Viallard et al. (2006) showed a correlation between $CD8^+$HLA-DR^+ T cells with low numbers of $CD19^+CD27^+$ memory B cells [24].

An increase in a subgroup of $CD8^+$T cells with cytotoxic effector memory expression markers are reported in CVID patients. These $CCR7^-$ T cells are similar to chronically activated T cells with impaired proliferation response [71]. Within the $CD8^+$ T cell subpopulation, $CD8^+$ effector memory has significantly lower frequency in organ-specific autoimmune disease, whereas $CD8^+$ terminally differentiated are significantly higher in the polyclonal lymphoproliferation and autoimmune cytopenias groups of clinically subdivided CVID patients [13].

In conclusion, $CD8^+$ T cell abnormalities specially increased levels of activated $CD8^+$ T-cells in CVID patients, might be associated with clinical manifestations or even viral infections, which commonly observed in these patients.

doi: 10.18176/jiaci.0069

7. T cell signaling defects in CVID

Recently, several studies demonstrated signaling defects in immune cells of CVID patients (**Table 3**). These include defects in TCR dependent signal transduction [72], BCR signaling [73], TLR signaling [74], and FcγRIIa signaling-associated molecules [75].

7.1. T cell signaling-associated surface molecules and consequence defects

Defect in TCR signal transduction and activation in CVID patients has been demonstrated in several studies. It has been revealed a deficiency in IL-2 and IFN-γ release upon TCR activation by various stimuli which have founded in $CD4^+$ T cells [76]. Other studies reported defective TCR and co-stimulatory (CD40L) molecules activation in $CD4^+$ and $CD8^+$ T cells [72, 77]. CD40L have important role in delivering functional signals in both $CD4^+$ and $CD8^+$ T cells [78], as defect in the amplification of TCR-derived activation by co-stimulatory signals could be responsible for impaired T-cell activation as well as defective amplification of the TCR-dependent signal transduction in CVID patients [79, 80]. Aspalter et al. (2007) found also a significant selective impairment in TNF-Receptor II (TNF-R II) co-stimulatory signaling events, which resulted in reduced TRAF1 expression and TCR/TNF-RII-driven T-cell proliferation [81]. The above mentioned studies proposed defects of TCR signaling and co-stimulation, thereby helping to understand the molecular basis of T-cell defects in CVID patients [82]. It would be conceivable that the reduced co-stimulatory and signaling capacity of TCR may contribute to the impaired interaction of T and B cell, resulting to the hypogammaglobulinaemia in CVID patients.

7.2. T cell signaling-associated cytoplasmic molecules and consequence defects

In addition to defect in TCR and co-stimulatory molecule, several defects in cell signaling-associated cytoplasmic molecules such as lymphocyte-specific protein tyrosine kinase (LCK) [83], inositol-1,4,5-trisphosphate (IP3) [80], Vav [84], phospholipase C gamma-1 *(*PLCγ-1*)* [85], Calcium mobilization [76], protein kinase C-δ (*PKCδ*) [86] and LPS-responsive beige-like anchor (LRBA) [87] are also described in the pathogenesis of immunodeficiency. Although these new monogenic defects share clinical phenotypes with CVID, they could be considered as distinct entities that may occasionally be misdiagnosed as CVID [88].

doi: 10.18176/jiaci.0069

8. The effects of IGIV on T cell in CVID patients

The common treatment for CVID is IgG replacement, often given as IGIV. Recent evidence shows that immune reconstitution treatment with IGIV has diverse effects on the immune system of CVID patients [89-91]. It is revealed that IGIV therapy resulted in elevation of the percentages of $CD4^+$ T cells [92], correction of CD4/CD8 inverse ratio and improvement of T cell function [93]. Paquin-Proulx et al. (2013) showed that immunotherapy with IGIV in CVID patients alleviates the state of persistent immune activation and suppressed $CD4^+$ T cell counts [94]. $CD4^+$ T cells in CVID patients have elevated levels of Ki67, CD38, and HLA-DR as the activation markers, PD-1 and CTLA-4 as exhaustion markers. It is revealed that the expression levels of activation and exhaustion markers remained elevated for up to one year on IGIV treatment [94]. Paradoxically, a study showed that IGIV treatment could reduce PD-1 expression on $CD4^+$ T cells and improve their response to bacterial infections [37].

In addition, an increase in Tregs was reported 30 min after IGIV infusion in CVID patients [92]. This elevation seems to be transient, because no sustained effect of IGIV therapy on Treg cell counts was observed between samples obtained at baseline and up to one year after initiation of IGIV infusion [94]. On the other hand, the frequency of iNKT cells as another subset of T cells with suppressor function does not restore and HLA-DR remains elevated following IGIV therapy. However, expression of PD-1 and CD161 is reduced when CVID patients are under IGIV treatment [94]. This data indicate that IGIV can attenuate iNKT cell activation and exhaustion in CVID patients.

CVID patients have higher plasma levels of IL-2 and IL-10 as well as a higher expression of FcγRIIb on $CD19^+$ B cells before IGIV infusion. It is demonstrated that the infusion of IGIV lead to further increases in the plasma levels of these cytokines 30 minutes after the termination of the infusion [92]. In addition, a significant increase in IL-2 expression in $CD4^+$ T cells and an increase in TNF-α expression in $CD8^+$ T cells has been reported following IGIV in CVID patients, while IFN-γ and expression of activation marker CD69 were not affected by IGIV infusion [95].

Similar to what was listed for the $CD4^+$ T cell, $CD8^+$ T cells in treatment-naive CVID have increased expression of activation markers Ki67 and co-expression of CD38 and

doi: 10.18176/jiaci.0069

HLA-DR [94]. It is showed that IGIV therapy reduces the expression of activation markers Ki67, CD38, and HLA-DR on $CD8^+$ T cells [94]. However, Artac et al. (2010) reported CD69 and HLA-DR expressions of $CD8^+$ T cells are not affected by IGIV infusion [96]. The immunological mechanisms by which IGIV can normalize T cell counts and function in CVID patients remains unclear, but Dolcino et al. (2014) reported that lower expression of LEPR, a gene important for $CD4^+$ T cell proliferation, was normalized after IGIV treatment in this patients [97]. Other results showed that IGIV replacement causes an increase in the CD95 and CD25 expressions in CVID patients. Recent report suggests that the CD95 may have a critical role in the effects of IGIV for control of autoimmunity and inflammation in CVID patients [96].

Totally, IGIV infusion resulted in elevation of the percentages of $CD4^+$ T cells and serum level of some cytokine after the infusion. However, this effect has not seen on the all T cell subsets. As, some compartments of immune cells such as Tregs and iNKT cells are not restoring after initiation of IGIV. Therefore, loss of these immune cells may clarifying why some of CVID patients despite the IGIV therapy still suffer from severe inflammatory complications [89]. In addition, it is possible that the loss of these cells is a predisposing factor in CVID patients to increase risks of autoimmunity including autoimmune enteropathy and interstitial lung disease.

9. Conclusion

Although CVID primarily characterized by hypogammaglobulinaemia and failure of specific antibody production as a result of B cell defects, a wide range of T cell abnormalities have been described in patients. According to essential dependence of normal function of B cell to T cell, it should be noted that many defects observed in CVID is due to T cell dysfunction, hence T cells my play a key role in the pathogenesis of CVID. Therefore, a proper classification for CVID by focus in more detailed genetic and immunologic features (phenotypic and functional characterization of B cells and evaluation of T cell function and frequency) along with clinical phenotypes of patients is required.

Conflict of interest

The authors declare no conflict of interest.

doi: 10.18176/jiaci.0069

References

1. Ahn, S. and Cunningham-Rundles, C., Role of B cells in common variable immune deficiency. Expert Rev Clin Immunol, 2009. **5**(5): p. 557-64.
2. Mohammadinejad, P., Pourhamdi, S., Abolhassani, H., Mirminachi, B., Havaei, A., Masoom, S.N., Sadeghi, B., Ghajar, A., Afarideh, M., Parvaneh, N., Mirsaeed-Ghazi, B., Movahedi, M., Gharagozlou, M., Chavoushzadeh, Z., Mahdaviani, A., Zandieh, F., Sherkat, R., Sadeghi-Shabestari, M., Faridhosseini, R., Jabbari-Azad, F., Ahanchian, H., Zandkarimi, M., Cherghi, T., Fayezi, A., Mohammadzadeh, I., Amin, R., Aleyasin, S., Moghtaderi, M., Ghaffari, J., Bemanian, M., Shafiei, A., Kalantari, N., Ahmadiafshar, A., Khazaei, H.A., Mohammadi, J., Nabavi, M., Rezaei, N., and Aghamohammadi, A., Primary Antibody Deficiency in a Tertiary Referral Hospital: A 30-Year Experiment. J Investig Allergol Clin Immunol, 2015. **25**(6): p. 416-25.
3. Conley, M.E., Notarangelo, L.D., and Etzioni, A., Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol, 1999. **93**(3): p. 190-7.
4. Seppanen, M., Aghamohammadi, A., and Rezaei, N., Is there a need to redefine the diagnostic criteria for common variable immunodeficiency? Expert Rev Clin Immunol, 2014. **10**(1): p. 1-5.
5. Karakoc-Aydiner, E., Ozen, A.O., Baris, S., Ercan, H., Ozdemir, C., and Barlan, I.B., Alteration in humoral immunity is common among family members of patients with common variable immunodeficiency. J Investig Allergol Clin Immunol, 2014. **24**(5): p. 346-51.
6. Nemati, S., Amirzargar, A.A., Farhadi, E., Hirbod-Mobarakeh, A., Nabavi, M., Soltani, S., Mahdaviani, S.A., Shahinpour, S., Arshi, S., MirAhmadian, M., Nicknam, M.H., Aghamohammadi, A., and Rezaei, N., RAD50 Single-Nucleotide Polymorphism in Predominantly Antibody Deficiency. J Investig Allergol Clin Immunol, 2015. **25**(4): p. 299-301.
7. Chapel, H., Lucas, M., Lee, M., Bjorkander, J., Webster, D., Grimbacher, B., Fieschi, C., Thon, V., Abedi, M.R., and Hammarstrom, L., Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood, 2008. **112**(2): p. 277-86.
8. Chapel, H., Lucas, M., Patel, S., Lee, M., Cunningham-Rundles, C., Resnick, E., Gerard, L., and Oksenhendler, E., Confirmation and improvement of criteria for clinical phenotyping in common variable immunodeficiency disorders in replicate cohorts. J Allergy Clin Immunol, 2012. **130**(5): p. 1197-1198 e9.
9. Mohammadinejad, P., Aghamohammadi, A., Abolhassani, H., Sadaghiani, M.S., Abdollahzade, S., Sadeghi, B., Soheili, H., Tavassoli, M., Fathi, S.M., Tavakol, M., Behniafard, N., Darabi, B., Pourhamdi, S., and Rezaei, N., Pediatric patients with common variable immunodeficiency: long-term follow-up. J Investig Allergol Clin Immunol, 2012. **22**(3): p. 208-14.
10. Aghamohammadi, A., Farhoudi, A., Moin, M., Rezaei, N., Kouhi, A., Pourpak, Z., Yaseri, N., Movahedi, M., Gharagozlou, M., Zandieh, F., Yazadni, F., Arshi, S., Mohammadzadeh, I., Ghazi, B.M., Mahmoudi, M., Tahaei, S., and Isaeian, A., Clinical and immunological features of 65 Iranian patients with common variable immunodeficiency. Clin Diagn Lab Immunol, 2005. **12**(7): p. 825-32.
11. Khodadad, A., Aghamohammadi, A., Parvaneh, N., Rezaei, N., Mahjoob, F., Bashashati, M., Movahedi, M., Fazlollahi, M.R., Zandieh, F., Roohi, Z.,

doi: 10.18176/jiaci.0069

Abdollahzade, S., Salavati, A., Kouhi, A., Talebpour, B., and Daryani, N.E., Gastrointestinal manifestations in patients with common variable immunodeficiency. Dig Dis Sci, 2007. **52**(11): p. 2977-83.

12. Giovannetti, A., Pierdominici, M., Mazzetta, F., Marziali, M., Renzi, C., Mileo, A.M., De Felice, M., Mora, B., Esposito, A., Carello, R., Pizzuti, A., Paggi, M.G., Paganelli, R., Malorni, W., and Aiuti, F., Unravelling the complexity of T cell abnormalities in common variable immunodeficiency. J Immunol, 2007. **178**(6): p. 3932-43.
13. Bateman, E.A., Ayers, L., Sadler, R., Lucas, M., Roberts, C., Woods, A., Packwood, K., Burden, J., Harrison, D., Kaenzig, N., Lee, M., Chapel, H.M., and Ferry, B.L., T cell phenotypes in patients with common variable immunodeficiency disorders: associations with clinical phenotypes in comparison with other groups with recurrent infections. Clin Exp Immunol, 2012. **170**(2): p. 202-11.
14. Kutukculer, N., Azarsiz, E., Aksu, G., and Karaca, N.E., Cd4+Cd25+Foxp3+ T regulatory cells, Th1 (Ccr5, Il-2, Ifn-Gamma) and Th2 (Ccr4, Il-4, Il-13) type chemokine receptors and intracellular cytokines in children with common variable immunodeficiency. Int J Immunopathol Pharmacol, 2015.
15. Boileau, J., Mouillot, G., Gerard, L., Carmagnat, M., Rabian, C., Oksenhendler, E., Pasquali, J.L., and Korganow, A.S., Autoimmunity in common variable immunodeficiency: correlation with lymphocyte phenotype in the French DEFI study. J Autoimmun, 2011. **36**(1): p. 25-32.
16. Rezaei, N., Wing, J.B., Aghamohammadi, A., Carlring, J., Lees, A., Asgarian-Omran, H., Pourpak, Z., Sarrafnejad, A., Kardar, G.A., Shahrestani, T., Masoumi, F., Zare, A., Saghafi, S., Sarrafzadeh, S., Foster, R.A., Heath, A.W., and Read, R.C., B-cell-T-cell activation and interaction in common variable immunodeficiency. Hum Immunol, 2010. **71**(4): p. 355-62.
17. Abolhassani, H., Amirkashani, D., Parvaneh, N., Mohammadinejad, P., Gharib, B., Shahinpour, S., Hirbod-Mobarakeh, A., Mirghorbani, M., Movahedi, M., Gharagozlou, M., Rezaei, N., and Aghamohammadi, A., Autoimmune phenotype in patients with common variable immunodeficiency. J Investig Allergol Clin Immunol, 2013. **23**(5): p. 323-9.
18. Ameratunga, R., Brewerton, M., Slade, C., Jordan, A., Gillis, D., Steele, R., Koopmans, W., and Woon, S.T., Comparison of diagnostic criteria for common variable immunodeficiency disorder. Front Immunol, 2014. **5**: p. 415.
19. Wada, T., Toma, T., Yasui, M., Inoue, M., Kawa, K., Imai, K., Morio, T., and Yachie, A., Different Clinical Phenotypes in 2 Siblings With X-Linked Severe Combined Immunodeficiency. J Investig Allergol Clin Immunol, 2016. **26**(1): p. 63-5.
20. Abolhassani, H., Cheraghi, T., Rezaei, N., Aghamohammadi, A., and Hammarstrom, L., Common Variable Immunodeficiency or Late-Onset Combined Immunodeficiency: A New Hypomorphic JAK3 Patient and Review of the Literature. J Investig Allergol Clin Immunol, 2015. **25**(3): p. 218-20.
21. Vukmanovic, S., Vuckovic, S., Stosic-Grujicic, S., Ramic, Z., and Abinun, M., An unusual T-cell surface phenotype in vivo correlates with the failure to proliferate and produce IL-2 in vitro in a patient with common variable immunodeficiency. Clin Immunol Immunopathol, 1992. **65**(3): p. 261-70.
22. Nordoy, I., Muller, F., Aukrust, P., and Froland, S.S., Adhesion molecules in common variable immunodeficiency (CVID)--a decrease in L-selectin-positive T lymphocytes. Clin Exp Immunol, 1998. **114**(2): p. 258-63.

doi: 10.18176/jiaci.0069

23. Baumert, E., Wolff-Vorbeck, G., Schlesier, M., and Peter, H.H., Immunophenotypical alterations in a subset of patients with common variable immunodeficiency (CVID). Clin Exp Immunol, 1992. **90**(1): p. 25-30.
24. Viallard, J.F., Blanco, P., Andre, M., Etienne, G., Liferman, F., Neau, D., Vidal, E., Moreau, J.F., and Pellegrin, J.L., CD8+HLA-DR+ T lymphocytes are increased in common variable immunodeficiency patients with impaired memory B-cell differentiation. Clin Immunol, 2006. **119**(1): p. 51-8.
25. Vlkova, M., Thon, V., Sarfyova, M., Blaha, L., Svobodnik, A., Lokaj, J., and Litzman, J., Age dependency and mutual relations in T and B lymphocyte abnormalities in common variable immunodeficiency patients. Clin Exp Immunol, 2006. **143**(2): p. 373-9.
26. Rezaei, N., Amirzargar, A.A., Shakiba, Y., Mahmoudi, M., Moradi, B., and Aghamohammadi, A., Proinflammatory cytokine gene single nucleotide polymorphisms in common variable immunodeficiency. Clin Exp Immunol, 2009. **155**(1): p. 21-7.
27. Rivoisy, C., Gerard, L., Boutboul, D., Malphettes, M., Fieschi, C., Durieu, I., Tron, F., Masseau, A., Bordigoni, P., Alric, L., Haroche, J., Hoarau, C., Berezne, A., Carmagnat, M., Mouillot, G., and Oksenhendler, E., Parental consanguinity is associated with a severe phenotype in common variable immunodeficiency. J Clin Immunol, 2012. **32**(1): p. 98-105.
28. Malphettes, M., Gerard, L., Carmagnat, M., Mouillot, G., Vince, N., Boutboul, D., Berezne, A., Nove-Josserand, R., Lemoing, V., Tetu, L., Viallard, J.F., Bonnotte, B., Pavic, M., Haroche, J., Larroche, C., Brouet, J.C., Fermand, J.P., Rabian, C., Fieschi, C., and Oksenhendler, E., Late-onset combined immune deficiency: a subset of common variable immunodeficiency with severe T cell defect. Clin Infect Dis, 2009. **49**(9): p. 1329-38.
29. Aghamohammadi, A., Abolhassani, H., Moazzami, K., Parvaneh, N., and Rezaei, N., Correlation between common variable immunodeficiency clinical phenotypes and parental consanguinity in children and adults. J Investig Allergol Clin Immunol, 2010. **20**(5): p. 372-9.
30. Arshi, S., Nabavi, M., Bemanian, M.H., Shakeri, R., Taghvaei, B., Ghalebaghi, B., Babaie, D., Bahrami, A., Fallahpour, M., Esmaeilzadeh, H., Rekabi, M., Amadian, J., Eslami, N., Shokri, S., Jalali, F., Akbarpour, N., Molatefi, R., and Rezaei, N., Phenotyping and follow up of forty-seven Iranian patients with common variable immunodeficiency. Allergol Immunopathol (Madr), 2015.
31. Cheraghi, T., Aghamohammadi, A., Mirminachi, B., Keihanian, T., Hedayat, E., Abolhassani, H., Sagvand, B.T., and Rezaei, N., Prediction of the evolution of common variable immunodeficiency: HLA typing for patients with selective IgA deficiency. J Investig Allergol Clin Immunol, 2014. **24**(3): p. 198-200.
32. Serana, F., Chiarini, M., Zanotti, C., Sottini, A., Bertoli, D., Bosio, A., Caimi, L., and Imberti, L., Use of V(D)J recombination excision circles to identify T- and B-cell defects and to monitor the treatment in primary and acquired immunodeficiencies. J Transl Med, 2013. **11**: p. 119.
33. Kamae, C., Nakagawa, N., Sato, H., Honma, K., Mitsuiki, N., Ohara, O., Kanegane, H., Pasic, S., Pan-Hammarstrom, Q., van Zelm, M.C., Morio, T., Imai, K., and Nonoyama, S., Common variable immunodeficiency classification by quantifying T-cell receptor and immunoglobulin kappa-deleting recombination excision circles. J Allergy Clin Immunol, 2013. **131**(5): p. 1437-40 e5.

doi: 10.18176/jiaci.0069

34. Lee, W.I., Huang, J.L., Lin, S.J., Yeh, K.W., Chen, L.C., Ou, L.S., Yao, T.C., Jaing, T.H., Shih, Y.F., Tseng, T.Y., and Lin, Y.L., Applying T-cell receptor excision circles and immunoglobulin kappa-deleting recombination excision circles to patients with primary immunodeficiency diseases. Ann Med, 2014. **46**(7): p. 555-65.
35. Oraei, M., Aghamohammadi, A., Rezaei, N., Bidad, K., Gheflati, Z., Amirkhani, A., Abolhassani, H., and Massoud, A., Naive CD4+ T cells and recent thymic emigrants in common variable immunodeficiency. J Investig Allergol Clin Immunol, 2012. **22**(3): p. 160-7.
36. Arandi, N., Mirshafiey, A., Jeddi-Tehrani, M., Abolhassani, H., Sadeghi, B., Mirminachi, B., Shaghaghi, M., and Aghamohammadi, A., Evaluation of CD4+CD25+FOXP3+ regulatory T cells function in patients with common variable immunodeficiency. Cell Immunol, 2013. **281**(2): p. 129-33.
37. Perreau, M., Vigano, S., Bellanger, F., Pellaton, C., Buss, G., Comte, D., Roger, T., Lacabaratz, C., Bart, P.A., Levy, Y., and Pantaleo, G., Exhaustion of bacteria-specific CD4 T cells and microbial translocation in common variable immunodeficiency disorders. J Exp Med, 2014. **211**(10): p. 2033-45.
38. Mouillot, G., Carmagnat, M., Gerard, L., Garnier, J.L., Fieschi, C., Vince, N., Karlin, L., Viallard, J.F., Jaussaud, R., Boileau, J., Donadieu, J., Gardembas, M., Schleinitz, N., Suarez, F., Hachulla, E., Delavigne, K., Morisset, M., Jacquot, S., Just, N., Galicier, L., Charron, D., Debre, P., Oksenhendler, E., and Rabian, C., B-cell and T-cell phenotypes in CVID patients correlate with the clinical phenotype of the disease. J Clin Immunol, 2010. **30**(5): p. 746-55.
39. Yazdani, R., Hakemi, M.G., Sherkat, R., Homayouni, V., and Farahani, R., Genetic defects and the role of helper T-cells in the pathogenesis of common variable immunodeficiency. Adv Biomed Res, 2014. **3**: p. 2.
40. Aghamohammadi, A., Abolhassani, H., Latif, A., Tabassomi, F., Shokuhfar, T., Torabi Sagvand, B., Shahinpour, S., Mirminachi, B., Parvaneh, N., Movahedi, M., Gharagozlou, M., Sherkat, R., Amin, R., Aleyasin, S., Faridhosseini, R., Jabbari-Azad, F., Cheraghi, T., Eslamian, M.H., Khalili, A., Kalantari, N., Shafiei, A., Dabbaghzade, A., Khayatzadeh, A., Ebrahimi, M., Razavinejad, D., Bazregari, S., Ghaffari, J., Bemanian, M.H., Behniafard, N., Kashef, S., Mohammadzadeh, I., Hammarstrom, L., and Rezaei, N., Long-term evaluation of a historical cohort of Iranian common variable immunodeficiency patients. Expert Rev Clin Immunol, 2014. **10**(10): p. 1405-17.
41. Goldacker, S. and Warnatz, K., Tackling the heterogeneity of CVID. Curr Opin Allergy Clin Immunol, 2005. **5**(6): p. 504-9.
42. Livaditi, O., Giamarellos-Bourboulis, E.J., Kakkas, I., Kapsimali, V., Lymberi, P., Papastariades, C., and Douzinas, E.E., Grouping of patients with common variable immunodeficiency based on immunoglobulin biosynthesis: comparison with a classification system on CD4-naive cells. Immunol Lett, 2007. **114**(2): p. 103-9.
43. Carbone, J., Sarmiento, E., Micheloud, D., Rodriguez-Molina, J., and Fernandez-Cruz, E., Elevated levels of activated CD4 T cells in common variable immunodeficiency: association with clinical findings. Allergol Immunopathol (Madr), 2006. **34**(4): p. 131-5.
44. Vlkova, M., Ticha, O., Nechvatalova, J., Kalina, T., Litzman, J., Mauri, C., and Blair, P.A., Regulatory B cells in CVID patients fail to suppress multifunctional IFN-gammaTNF-alphaCD4 T cells differentiation. Clin Immunol, 2015. **160**(2): p. 292-300.

doi: 10.18176/jiaci.0069

45. Rezaei, N., Aghamohammadi, A., Nourizadeh, M., Kardar, G.A., Pourpak, Z., Zare, A., and Read, R.C., Cytokine production by activated T cells in common variable immunodeficiency. J Investig Allergol Clin Immunol, 2010. **20**(3): p. 244-51.
46. Warnatz, K., Wehr, C., Drager, R., Schmidt, S., Eibel, H., Schlesier, M., and Peter, H.H., Expansion of CD19(hi)CD21(lo/neg) B cells in common variable immunodeficiency (CVID) patients with autoimmune cytopenia. Immunobiology, 2002. **206**(5): p. 502-13.
47. Compeer, E.B., Janssen, W., van Royen-Kerkhof, A., van Gijn, M., van Montfrans, J.M., and Boes, M., Dysfunctional BLK in common variable immunodeficiency perturbs B-cell proliferation and ability to elicit antigen-specific CD4+ T-cell help. Oncotarget, 2015. **6**(13): p. 10759-71.
48. Barbosa, R.R., Silva, S.P., Silva, S.L., Melo, A.C., Pedro, E., Barbosa, M.P., Pereira-Santos, M.C., Victorino, R.M., and Sousa, A.E., Primary B-cell deficiencies reveal a link between human IL-17-producing CD4 T-cell homeostasis and B-cell differentiation. PLoS One, 2011. **6**(8): p. e22848.
49. Ganjalikhani-Hakemi, M., Yazdani, R., Sherkat, R., Homayouni, V., Masjedi, M., and Hosseini, M., Evaluation of the T helper 17 cell specific genes and the innate lymphoid cells counts in the peripheral blood of patients with the common variable immunodeficiency. J Res Med Sci, 2014. **19**(Suppl 1): p. S30-5.
50. Hsu, H.C., Yang, P., Wang, J., Wu, Q., Myers, R., Chen, J., Yi, J., Guentert, T., Tousson, A., Stanus, A.L., Le, T.V., Lorenz, R.G., Xu, H., Kolls, J.K., Carter, R.H., Chaplin, D.D., Williams, R.W., and Mountz, J.D., Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice. Nat Immunol, 2008. **9**(2): p. 166-75.
51. Romberg, N., Hsu, I., Price, C., Cunningham-Rundles, C., and Meffre, E., Expansion Of Circulating T Follicular Helper Cells In CVID Patients With Autoimmune Cytopenias. Journal of Allergy and Clinical Immunology, 2014. **133**(2): p. AB162.
52. Wang, L.J., Qu, W., and Shao, Z.H., [Advance of researches on relation of Th17 cells with immuno-associatied hematologic diseases]. Zhongguo Shi Yan Xue Ye Xue Za Zhi, 2014. **22**(6): p. 1766-70.
53. Azizi, G., Jadidi-Niaragh, F., and Mirshafiey, A., Th17 Cells in Immunopathogenesis and treatment of rheumatoid arthritis. Int J Rheum Dis, 2013. **16**(3): p. 243-53.
54. Marinoni, B., Ceribelli, A., Massarotti, M.S., and Selmi, C., The Th17 axis in psoriatic disease: pathogenetic and therapeutic implications. Auto Immun Highlights, 2014. **5**(1): p. 9-19.
55. Biswas, P.S., Aggarwal, R., Levesque, M.C., Maers, K., and Ramani, K., Type I interferon and T helper 17 cells co-exist and co-regulate disease pathogenesis in lupus patients. Int J Rheum Dis, 2015. **18**(6): p. 646-53.
56. Hel, Z., Huijbregts, R.P., Xu, J., Nechvatalova, J., Vlkova, M., and Litzman, J., Altered serum cytokine signature in common variable immunodeficiency. J Clin Immunol, 2014. **34**(8): p. 971-8.
57. Mannon, P.J., Fuss, I.J., Dill, S., Friend, J., Groden, C., Hornung, R., Yang, Z., Yi, C., Quezado, M., Brown, M., and Strober, W., Excess IL-12 but not IL-23 accompanies the inflammatory bowel disease associated with common variable immunodeficiency. Gastroenterology, 2006. **131**(3): p. 748-56.
58. Rezaei, N., Aghamohammadi, A., Kardar, G.A., Nourizadeh, M., and Pourpak, Z., T-helper 1 and 2 cytokine assay in patients with common variable immunodeficiency. J Investig Allergol Clin Immunol, 2008. **18**(6): p. 449-53.

doi: 10.18176/jiaci.0069

59. Varzaneh, F.N., Keller, B., Unger, S., Aghamohammadi, A., Warnatz, K., and Rezaei, N., Cytokines in common variable immunodeficiency as signs of immune dysregulation and potential therapeutic targets - a review of the current knowledge. J Clin Immunol, 2014. **34**(5): p. 524-43.
60. Del Vecchio, G.C., Martire, B., Lassandro, G., Cecinati, V., De Mattia, D., Ciccarelli, M., Piacente, L., and Giordano, P., Reduced interleukin-5 production by peripheral CD4+ T cells in common variable immunodeficiency patients. Immunopharmacol Immunotoxicol, 2008. **30**(4): p. 679-86.
61. Arumugakani, G., Wood, P.M., and Carter, C.R., Frequency of Treg cells is reduced in CVID patients with autoimmunity and splenomegaly and is associated with expanded CD21lo B lymphocytes. J Clin Immunol, 2010. **30**(2): p. 292-300.
62. Melo, K.M., Carvalho, K.I., Bruno, F.R., Ndhlovu, L.C., Ballan, W.M., Nixon, D.F., Kallas, E.G., and Costa-Carvalho, B.T., A decreased frequency of regulatory T cells in patients with common variable immunodeficiency. PLoS One, 2009. **4**(7): p. e6269.
63. Yu, G.P., Chiang, D., Song, S.J., Hoyte, E.G., Huang, J., Vanishsarn, C., and Nadeau, K.C., Regulatory T cell dysfunction in subjects with common variable immunodeficiency complicated by autoimmune disease. Clin Immunol, 2009. **131**(2): p. 240-53.
64. Arandi, N., Mirshafiey, A., Abolhassani, H., Jeddi-Tehrani, M., Edalat, R., Sadeghi, B., Shaghaghi, M., and Aghamohammadi, A., Frequency and expression of inhibitory markers of CD4(+) CD25(+) FOXP3(+) regulatory T cells in patients with common variable immunodeficiency. Scand J Immunol, 2013. **77**(5): p. 405-12.
65. Horn, J., Manguiat, A., Berglund, L.J., Knerr, V., Tahami, F., Grimbacher, B., and Fulcher, D.A., Decrease in phenotypic regulatory T cells in subsets of patients with common variable immunodeficiency. Clin Exp Immunol, 2009. **156**(3): p. 446-54.
66. Genre, J., Errante, P.R., Kokron, C.M., Toledo-Barros, M., Camara, N.O., and Rizzo, L.V., Reduced frequency of CD4(+)CD25(HIGH)FOXP3(+) cells and diminished FOXP3 expression in patients with Common Variable Immunodeficiency: a link to autoimmunity? Clin Immunol, 2009. **132**(2): p. 215-21.
67. Holm, A.M., Aukrust, P., Aandahl, E.M., Muller, F., Tasken, K., and Froland, S.S., Impaired secretion of IL-10 by T cells from patients with common variable immunodeficiency--involvement of protein kinase A type I. J Immunol, 2003. **170**(11): p. 5772-7.
68. Carter, C.R., Aravind, G., Smalle, N.L., Cole, J.Y., Savic, S., and Wood, P.M., CVID patients with autoimmunity have elevated T cell expression of granzyme B and HLA-DR and reduced levels of Treg cells. J Clin Pathol, 2013. **66**(2): p. 146-50.
69. Viallard, J.F., Ruiz, C., Guillet, M., Pellegrin, J.L., and Moreau, J.F., Perturbations of the CD8(+) T-cell repertoire in CVID patients with complications. Results Immunol, 2013. **3**: p. 122-8.
70. Lanio, N., Sarmiento, E., Gallego, A., and Carbone, J., Immunophenotypic profile of T cells in common variable immunodeficiency: is there an association with different clinical findings? Allergol Immunopathol (Madr), 2009. **37**(1): p. 14-20.
71. Holm, A.M., Sivertsen, E.A., Tunheim, S.H., Haug, T., Bjerkeli, V., Yndestad, A., Aukrust, P., and Froland, S.S., Gene expression analysis of peripheral T cells in a subgroup of common variable immunodeficiency shows predominance of CCR7(-) effector-memory T cells. Clin Exp Immunol, 2004. **138**(2): p. 278-89.

doi: 10.18176/jiaci.0069

72. Thon, V., Wolf, H.M., Sasgary, M., Litzman, J., Samstag, A., Hauber, I., Lokaj, J., and Eibl, M.M., Defective integration of activating signals derived from the T cell receptor (TCR) and costimulatory molecules in both CD4+ and CD8+ T lymphocytes of common variable immunodeficiency (CVID) patients. Clin Exp Immunol, 1997. **110**(2): p. 174-81.
73. Schwartz, R., Porat, Y.B., Handzel, Z., Sthoeger, Z., Garty, B.Z., Confino-Cohen, R., Levy, J., and Zan-Bar, I., Identification of a subset of common variable immunodeficiency patients with impaired B-cell protein tyrosine phosphorylation. Clin Diagn Lab Immunol, 1999. **6**(6): p. 856-60.
74. Yu, J.E., Knight, A.K., Radigan, L., Marron, T.U., Zhang, L., Sanchez-Ramon, S., and Cunningham-Rundles, C., Toll-like receptor 7 and 9 defects in common variable immunodeficiency. J Allergy Clin Immunol, 2009. **124**(2): p. 349-56, 356 e1-3.
75. van der Heijden, J., Geissler, J., van Mirre, E., van Deuren, M., van der Meer, J.W., Salama, A., van den Berg, T.K., Roos, D., and Kuijpers, T.W., A novel splice variant of FcgammaRIIa: a risk factor for anaphylaxis in patients with hypogammaglobulinemia. J Allergy Clin Immunol, 2013. **131**(5): p. 1408-16 e5.
76. Fischer, M.B., Hauber, I., Eggenbauer, H., Thon, V., Vogel, E., Schaffer, E., Lokaj, J., Litzman, J., Wolf, H.M., Mannhalter, J.W., and et al., A defect in the early phase of T-cell receptor-mediated T-cell activation in patients with common variable immunodeficiency. Blood, 1994. **84**(12): p. 4234-41.
77. Farrington, M., Grosmaire, L.S., Nonoyama, S., Fischer, S.H., Hollenbaugh, D., Ledbetter, J.A., Noelle, R.J., Aruffo, A., and Ochs, H.D., CD40 ligand expression is defective in a subset of patients with common variable immunodeficiency. Proc Natl Acad Sci U S A, 1994. **91**(3): p. 1099-103.
78. Frentsch, M., Stark, R., Matzmohr, N., Meier, S., Durlanik, S., Schulz, A.R., Stervbo, U., Jurchott, K., Gebhardt, F., Heine, G., Reuter, M.A., Betts, M.R., Busch, D., and Thiel, A., CD40L expression permits CD8+ T cells to execute immunologic helper functions. Blood, 2013. **122**(3): p. 405-12.
79. Fischer, M.B., Hauber, I., Wolf, H.M., Vogel, E., Mannhalter, J.W., and Eibl, M.M., Impaired TCR signal transduction, but normal antigen presentation, in a patient with common variable immunodeficiency. Br J Haematol, 1994. **88**(3): p. 520-6.
80. Fischer, M.B., Wolf, H.M., Hauber, I., Eggenbauer, H., Thon, V., Sasgary, M., and Eibl, M.M., Activation via the antigen receptor is impaired in T cells, but not in B cells from patients with common variable immunodeficiency. Eur J Immunol, 1996. **26**(1): p. 231-7.
81. Aspalter, R.M., Eibl, M.M., and Wolf, H.M., Defective T-cell activation caused by impairment of the TNF receptor 2 costimulatory pathway in common variable immunodeficiency. J Allergy Clin Immunol, 2007. **120**(5): p. 1193-200.
82. Bergbreiter, A. and Salzer, U., Common variable immunodeficiency: a multifaceted and puzzling disorder. Expert Rev Clin Immunol, 2009. **5**(2): p. 167-80.
83. Sawabe, T., Horiuchi, T., Nakamura, M., Tsukamoto, H., Nakahara, K., Harashima, S.I., Tsuchiya, T., and Nakano, S., Defect of lck in a patient with common variable immunodeficiency. Int J Mol Med, 2001. **7**(6): p. 609-14.
84. Paccani, S.R., Boncristiano, M., Patrussi, L., Ulivieri, C., Wack, A., Valensin, S., Hirst, T.R., Amedei, A., Del Prete, G., Telford, J.L., D'Elios, M.M., and Baldari, C.T., Defective Vav expression and impaired F-actin reorganization in a subset of patients with common variable immunodeficiency characterized by T-cell defects. Blood, 2005. **106**(2): p. 626-34.

doi: 10.18176/jiaci.0069

85. Ombrello, M.J., Remmers, E.F., Sun, G., Freeman, A.F., Datta, S., Torabi-Parizi, P., Subramanian, N., Bunney, T.D., Baxendale, R.W., Martins, M.S., Romberg, N., Komarow, H., Aksentijevich, I., Kim, H.S., Ho, J., Cruse, G., Jung, M.Y., Gilfillan, A.M., Metcalfe, D.D., Nelson, C., O'Brien, M., Wisch, L., Stone, K., Douek, D.C., Gandhi, C., Wanderer, A.A., Lee, H., Nelson, S.F., Shianna, K.V., Cirulli, E.T., Goldstein, D.B., Long, E.O., Moir, S., Meffre, E., Holland, S.M., Kastner, D.L., Katan, M., Hoffman, H.M., and Milner, J.D., Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. N Engl J Med, 2012. **366**(4): p. 330-8.

86. Salzer, E., Santos-Valente, E., Klaver, S., Ban, S.A., Emminger, W., Prengemann, N.K., Garncarz, W., Mullauer, L., Kain, R., Boztug, H., Heitger, A., Arbeiter, K., Eitelberger, F., Seidel, M.G., Holter, W., Pollak, A., Pickl, W.F., Forster-Waldl, E., and Boztug, K., B-cell deficiency and severe autoimmunity caused by deficiency of protein kinase C delta. Blood, 2013. **121**(16): p. 3112-6.

87. Charbonnier, L.M., Janssen, E., Chou, J., Ohsumi, T.K., Keles, S., Hsu, J.T., Massaad, M.J., Garcia-Lloret, M., Hanna-Wakim, R., Dbaibo, G., Alangari, A.A., Alsultan, A., Al-Zahrani, D., Geha, R.S., and Chatila, T.A., Regulatory T-cell deficiency and immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like disorder caused by loss-of-function mutations in LRBA. J Allergy Clin Immunol, 2015. **135**(1): p. 217-27.

88. Al-Herz, W., Bousfiha, A., Casanova, J.L., Chatila, T., Conley, M.E., Cunningham-Rundles, C., Etzioni, A., Franco, J.L., Gaspar, H.B., Holland, S.M., Klein, C., Nonoyama, S., Ochs, H.D., Oksenhendler, E., Picard, C., Puck, J.M., Sullivan, K., and Tang, M.L., Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Front Immunol, 2014. **5**: p. 162.

89. Paquin-Proulx, D. and Sandberg, J.K., Persistent Immune Activation in CVID and the Role of IVIg in Its Suppression. Front Immunol, 2014. **5**: p. 637.

90. Azimi, M., Aghamohammadi, A., Ochs, H.D., and Rezaei, N., Soluble molecules in intravenous immunoglobulin: benefits and limitations. Expert Rev Clin Immunol, 2015: p. 1-3.

91. Abolhassani, H., Sagvand, B.T., Shokuhfar, T., Mirminachi, B., Rezaei, N., and Aghamohammadi, A., A review on guidelines for management and treatment of common variable immunodeficiency. Expert Rev Clin Immunol, 2013. **9**(6): p. 561-74; quiz 575.

92. Kasztalska, K., Ciebiada, M., Cebula-Obrzut, B., and Gorski, P., Intravenous immunoglobulin replacement therapy in the treatment of patients with common variable immunodeficiency disease: an open-label prospective study. Clin Drug Investig, 2011. **31**(5): p. 299-307.

93. Lu, W., Liu, Z.Y., and Li, T.S., [Common variable immunodeficiency: report of 12 cases and review of literature]. Zhonghua Nei Ke Za Zhi, 2008. **47**(5): p. 378-81.

94. Paquin-Proulx, D., Santos, B.A., Carvalho, K.I., Toledo-Barros, M., Barreto de Oliveira, A.K., Kokron, C.M., Kalil, J., Moll, M., Kallas, E.G., and Sandberg, J.K., IVIg immune reconstitution treatment alleviates the state of persistent immune activation and suppressed CD4 T cell counts in CVID. PLoS One, 2013. **8**(10): p. e75199.

95. Sewell, W.A., North, M.E., Cambronero, R., Webster, A.D., and Farrant, J., In vivo modulation of cytokine synthesis by intravenous immunoglobulin. Clin Exp Immunol, 1999. **116**(3): p. 509-15.

doi: 10.18176/jiaci.0069

96. Artac, H., Kara, R., and Reisli, I., In vivo modulation of the expressions of Fas and CD25 by intravenous immunoglobulin in common variable immunodeficiency. Clin Exp Med, 2010. **10**(1): p. 27-31.
97. Dolcino, M., Patuzzo, G., Barbieri, A., Tinazzi, E., Rizzi, M., Beri, R., Argentino, G., Ottria, A., Lunardi, C., and Puccetti, A., Gene expression profiling in peripheral blood mononuclear cells of patients with common variable immunodeficiency: modulation of adaptive immune response following intravenous immunoglobulin therapy. PLoS One, 2014. **9**(5): p. e97571.

Table 1. Different types of T lymphocytes

Type of cell	Subset	Characteristic Markers	Normal function	Associated pathologies
T CD4	**Th1**	T-bet, IFN-γ	Cell-mediated immunity, Antiviral and antimicrobial immunity	Autoimmunity, Susceptibility to intercellular pathogens
	Th2	STAT6, GATA3, IL-4, IL-5, IL-13	Immunity to extacellular parasites	Allergy and Asthma
	Th9	PU.1, IL-9	Protection against parasites infections	Allergy and Asthma
	Th17	RORγt, IL-17, CD161 (human)	Antimicrobial immunity, Protection at mucocutaneous sites,	Autoimmunity, Susceptibility to fungal infections
	Th22	AHR, IL-22	Barrier immunity, Enhancement of innate immunity, Tissue regeneration	Skin inflammation, Allergy, Autoimmunity and rheumatic disease
	TFH	BCL-6, IL-21	Help for B cell activation and differentiation, Generation of long-lived antibody responses	Humoral immunodeficiency, Autoimmunity, T cell lymphoma
	Treg	CD25, FoxP3, IL-10, TGF-β	Tolerance induction and immunosuppression	Autoimmunity, inflammatory conditions, Allergy and cancer
T CD8	**CTL**	CD3, CD8, Perforin and Granzyme	Killing of infected and transformed cells	Chronic hepatitis and Hepatocellular carcinoma
Innate like T-cell	**γδ T**	γδ TCR, CD3+, CD7+, CD2+, CD4-, CD8-	Pro- and anti-inflammatory functions in both innate and adaptive immunity.	Autoimmune and Inflammatory diseases
	NKT	CD161, CD56	Pro- and anti-inflammatory functions, Modulation of immune responses	Autoimmunity, allergy and Cancer,

Th, T helper; Treg, regulatory T cells; CTL, Cytotoxic T cell; NKT, Natural killer T; IFN, Interferon; IL, Interleukin; STAT, Signal Transducer and Activator of Transcription ; TGF-β; Transforming growth factor beta.

doi: 10.18176/jiaci.0069

Table 2. T cell defects and related manifestation in CVID

T cells	Frequency	Related manifestation in CVID	References
CD4+ T cells	↓Total ↓Naive ↑Activated ↓Memory	- Recurrent infection - Autoimmunity (especially autoimmune cytopenia) - Splenomegaly - Lymphoid proliferation - Poor response to protein antigens and vaccines	Bateman et al. 2012 Resnick et al. 2012 Carbone et al. 2006
	↓Th17 ↑Th1	- Germinal centers disruption - Negatively correlate with naive CD4+ T cells	Barbosa et al. 2011 Resnick et al. 2012 Moratto et al. 2006
	↓Treg	-Decrease in suppressive capacity of autoreactive effectors cell	Aghamohammadi et al.2005
CD8+ T cells	↓Total ↓Naive ↑Activated ↓Memory	- Susceptibility to viral infection - Polyclonal expansions of LGL -Increase in granzyme *B*	Carter et al. 2013 Holm et al. 2006 Baumert et al. 1992 Viallard et al. 2013 Kuntz et al. 2011
Innate like	↓iNKT	- Autoimmunity -Increase in IFNγ	Paquin-Proulx et al. 2014 Carvalho et al. 2010
	↑γδ-T	- Granulomatous lesions - Inflammation	Viallard et al.2002
CVID, Common variable immunodeficiency; Th, T helper; Treg, Regulatory T cell; iNKT, Invariant natural killer cell;LGL, large granular lymphocytes			

Table 3. Defective signaling molecules in T cells of CVID patients

Defective molecules	Normal function	Cause of defect	References
TCR signal transduction	T cell activation, development, proliferation and differentiation	Mutations	Fischer et al.
Lck	Regulation of T cell maturation, activation and differentiation	A defective splicing product of Ick gene and decrease in expression of lck	Sawabe et al.
IP3	Calcium releasing from endoplasmic reticulum	Defective TCR-mediated Ins(1,4,5)P3 formation	Fischer et al.
Vav expression and F-actin reorganization	T cell activation and reorganization of the T cell actin cytoskeleton	Impaired Vav expression and defective F-actin reorganization/ Mutations	Capitani et al
CTLA-4	negative regulator expressed on activated T cells and Treg cells	Mutations and low expression	Arandi et al.
Calcium mobilization	Cell proliferation and activation	Defective Calcium Flux	Fischer et al.
LRBA	Vesicle trafficking regulator required for CVID genes such as CD19, CD20 and BAFFR	Mutations	Charbonnier et al.
CARD11	B cell receptor- and T cell receptor-mediated activation of the IKK complex	Mutations	Stepensky et al.
PI3Kδ	development, activation and migration of B cells, T cells and NK cells	gain-of-function mutation in the *PIK3CD* gene	Elgizouli et al.

TCR; T-cell receptor, ZAP-70; Zeta-chain-associated protein kinase 70, LAT ; linker for activation of T cells, IP3; Inositol 1,4,5-triphosphate, CTLA-4; Cytotoxic T-lymphocyte-antigen 4, LRBA; Lipopolysaccharide-responsive beige-like Anchor, PI3Kδ ; Phosphatidylinositol-3-kinase delta, CARD11; Caspase recruitment domain family, member 11.