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A Study of the Roles of IL-17A and its Receptor in Iraqi EBV-positive Patients with Chronic Myeloid Leukemia

Wisal Salman Abd[1*] and Najah Salman Abd[2]

[1]Department of Biotechnology, College of Science, University of Baghdad, Baghdad, Iraq.
[2] Iraqi Center for Cardiac Diseases, Ghazi Alhariry Hospital, Baghdad, Iraq.

Abstract

This study aimed to investigate the correlation between Epstein Barr Virus (EBV) and leukemia, especially focusing on the involvement of Interleukin 17A and Interleukin 17A receptor. A sample of 53 patients with chronic myeloid leukemia (CML) infected with EBV and 30 healthy individuals was involved in the study. Levels of IL-17A and IL-17A R were estimated by using the enzyme-linked immunosorbent assay (ELISA) technique and viral load was estimated by the quantitative polymerase chain reaction (PCR). The mean viral load was 31.7, ranging from 27to 34.4, with significant differences between the patients and control groups (p=0.005). All patients (100%) were positive for EBV.The mean serum IL-17A level was 113.87ng/ml and the mean IL-17AR level was 180ng/ml. The value of Person Correlation Coefficient (*r*) between IL-17A and IL-17AR was 0.9, while the coefficient value between IL-17A and EBV viral load was 0.53, showing a significant correlation (p= 0.5). EBV, IL-17, and IL-17R have important roles in the pathogenesis and diagnosis of leukemia.

Key Words: Leukemia, EBV, IL-17A, IL-17R

*Email : wisalimmunology@gmail.com

دراسة ابيضاض الدم المزمن في بعض المرضى العراقيين

وصال سلمان عبد[1] , نجاح سلمان عبد[2]
قسم التقنيات الأحيائية , كلية العلوم, جامعة بغداد, بغداد , العراق
المركز االعراقي لامراض القلب ، مستشفى غازي الحريري ، بغداد ، العراق

الخلاصة

هدفت الدراسة الى التحري عن العلاقة بين فايروس الابشتاين بار ومرضى ابيضاض الدم بالتركيز على وجود الانترلوكين 17 ومستقبله .عدد المرضى في هذه الدراسة كان 53 وعدد الأصحاء 30 وقد تم فحص كل المرضى بالاختبارات التالية: الانترلوكين 17 ومستقبل الانترلوكين 17 وفايروس الابشتاين بار IgG و IgM بطريقة الاليزا وتم فحص كمية الفايروس بالطريقة الجزيئية تفاعل البلمرة.

متوسط كمية الفايروس كان 31.7 والمدى من 27-34.4 وكانت الفروقات معنوية بينه وبين الاصحاء p=0.005 وبالنسبة لفحص الفايروس الاليزا كانت النتائج ايجابية لكل المرضى وكان متوسط الانترلوكين 17 = 113.87 نانوكرام/مل ومتوسط مستقبل الانترلوكين 17 = 108 نانوكرام/مل اما معامل العلاقة بين الانترلوكين 17 و مستقبل الانترلوكين 17 =(0.9) وبين كمية الفايروس =(0.53) , نستنتج من ذلك ان كل من الانترلوكينات اعلاه وفايروس الابشتان لها علاقة بامراضية وتشخيص المرض.

1. Introduction

Chronic Myeloid Leukemia (CML) is a malignant blood disease which affects hematopoiesis of stem cells [1]. The main cause is genetic, where the presence of the Philadelphia chromosome causes the fusion of the BCR-ABL gene that encodes for a tyrosine kinase that becomes effectively stimulated. This gene has a benefit in the diagnosis and prognosis of this leukemia [2]. Twenty percent of leukemia cases worldwide were reported to be of the CML type. The exact reason for CML is unclear till now, whereas immunological and genetic factors may have a crucial role in the initiation of leukemia [3]. The incidence of CML covers an age range of 2 to 100 years, with a mean age of 55 years and a higher rate of ten percent observed in patients younger than 20 years, being higher in males than in females (1.4/1.3) [1]. As related to the clinical course, 45 percent of patients in the asymptomatic type demonstrate splenomegaly and higher count of WBCs, a condition termed as "left shift" [4]. However, ninety percent of CML patients develop a chronic phase, characterized by the symptoms of a loss of weight, fatigue, night sweating, fever, as well as splenomegaly that leads to distress in the abdomen, with 5 % developing hemorrhagic and thrombotic complications [5]. The more

advanced phase, i.e. the chronic phase, is not well understood, while some researchers believe that the reason is genomic [6]. According to the survival rate and the complete blood film, there are three groups of patients in the chronic phase 1984 [7]. Another classification of patients depends on prognostic factors, including the complete blood picture, size of the spleen, and age [8].

In terms of treatment, although CML therapy is in fast development, radiotherapy of the spleen is the treatment of choice since the 1960s [6,9,10]. No drug could silence the Philadelphia chromosome. One third of patients have no response to TKI (tyrosine kinase inhibitor) because they have a mutation to the ABL gene [11-13]. Regarding the immunology of the disease, the role of T lymphocytes is not very well understood, although the Th cells were reported to play a crucial role in autoimmune disorders as well as cancers (i.e., in the pathogenesis, development, and progression), Interleukins are cytokines that have a very important role in immune responses, including modulation, adhesion, proliferation, maturation, and migration of immune cells [11]. It is very complicated to estimate the exact functions of cytokines, since it is dependent on the type of celland type of immune response. There are four major groups of IL1-like cytokines, (IL4 - like, gamma-chain, and IL6/12 - like) cytokines, (IL10 - like and IL28 - like) cytokines, and the IL17-like cytokines. IL-17 is produced by Th 17 cells and has a unique CD4+ helper subset. IL 17 has a function during bacterial and fungal infections and a critical role in tumor progression and antitumor activity [13]. It is so sophisticated matter to estimate the exact function of cytokines, this is dependent on cell type and type of an immune response [14]. IL-17A is released by activated T lymphocytes and the complementary DNA (cDNA) when isolated and genetically engineered in hybridoma of murine exclusively from cytotoxic T cell CD8+ T cells (CTLA-8) [1,2] and when examined it was ahomology to open frame from T-lymphocyte from Herpes virus sàimiri. The product of the IL-17A gene has a sequence of 150 acids with a Molecular weight of15 Kilodalton, whereas, when released, it is

a disulfide bond dimer composed of glycoprotein with about 35 kilodalton [3]. The actions of IL-17 cytokines, as well as their receptors and forms, is of importance in the immune response, and homeostasis, and [13]. Receptors of IL-17A are expressed in all cells in all tissue types, while IL-17A is found only in T lymphocytes. The role of IL-17AR is to induce the cytokines involved in inflammation. A number of researchers described the biological role of Th17 in leukemias, during their investigation of the pathological processes involving ILs and their receptors, such as IL-17A, IL-17F, and IL-23 [15]. EBV is a herpesvirus that causes a persistent infection in human body and becomes lifelong latent in B cells [2,3]. If an adequate number of T cells is found, EBV loses the ability to proliferate, but with the reduction in the number of EBV-specific T cells, the virus proliferates and spreads, leading to a lymphoproliferative EBV-LPD [4]. Some proteins act as activators that can transfer the virus from latent mode to productive mode [5]. Many researchers stated that EBV has a role in triggering different malignancies of lymphocytes such as Burkitt's lymphoma and leukemias [7]. A wide range of studies proved the presence of EBV DNA in the blood of patients with leukemia [8]. Different tumors of lymphoid and epithelial cells, such as CLL as a well-defined lymphoid disease, have been associated with the pathology of this virus, in which the transformed cells produce the virus [15]. This virus is thought to be associated with well-defined tumors of the epithelium and lymph, where it acts as the driver of the transformation of the cancer cells [16]. The present article detects the possible correlation between EBV in leukemia patients and the levels of IL-17 and IL-17R.

2. Materials and Methods

2.1 Patients: Fifty-three patients with leukemia were included in this study, all were admitted to the Iraqi Center for Blood Diseases, Baghdad, Iraq.

Control: Thirty apparently healthy individuals were also included in this study.

2.2 Samples: Three millilitres of venous blood were withdrawn from patients, 2 ml of which were centrifuged at 3000x for 5 minutes. Serum samples were separated in 3 aliquots in Eppendorf tubes and kept frozen in a - 20˚C refrigerator until ELISA assay. Sera of patients were tested using specific kits for IL-17A (Elabscience), IL17A receptor (Elabscience), and EBV (ELISA, Vircell). The remaining sample (1 ml) was dispensed in an anticoagulant tube and frozen at -20 ^{0}C until the isolation of DNA for the test of viral load. The isolation of viral DNA was performed using a ready kit (Geneaid), followed by quantitation by using the RT-PCR technique (figure 1). The Data were analyzed using the ANOVA test by the SPSS statistical program (figure 2), with *P*- value <0.05 being considered as significant [18].

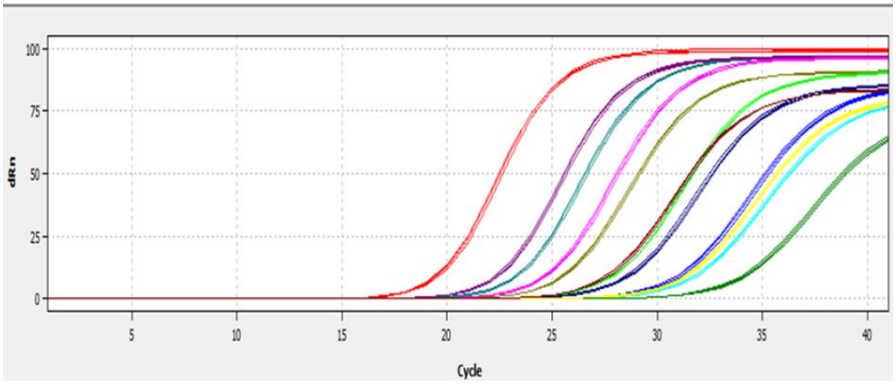

Figure (1): Amplification of DNA Using PCR

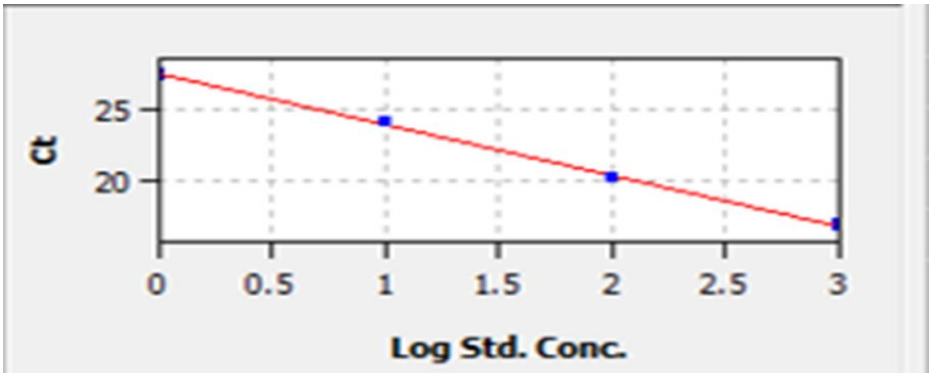

Figure (2): standard curve

3. Results and Discussion

The mean viral load value was 31.7, ranging from 27to 34.4, with significant differences between the patient and control groups (p=0.005). All patients (100%) were positive for EBV, as tested by the ELISA technique, while all healthy individuals were negative. In an earlier investigation, researchers proved that approximately 38% of leukaemia patients were infected with EBV [19]. IL-17A serum level of patients ranged from 46-350 and the mean value was 113.87 ng/ml, whereas in control the levels ranged from 7.92-18.51 and the mean value was 16.1ng/ml, with significant difference found between patients and control (p=0.001). IL-17AR level ranged from 90 to 400 and the mean value was 180 ng/ml, with a significant difference between patients and control *(P* = 0.0005). The Person Correlation Coefficient value between IL-17A and IL-17AR was found to be *r* = 0.9, whereas that between IL-17A and EBV viral load was *r* = 0.53, with the correlations being significant (p= 0.5). These results are consistent with those published by Husham, 2016, while they are in disagreement with those of Elsissy [20-21]. Several researchers stated that IL-17 groups and their receptors have a crucial role in tissue homeostasis in normal healthy individuals and patients with cancers [12, 22]. These researchers also proved that IL-17 protects the body against different infections and has a role in controlling various pathogens such as bacteria, parasites, fungi, etc. [12]. IL-17 family and their receptors and ligands mediate inflammation and the pathogenesis of the above-mentioned infections [22]. Han found, in 2014, that most leukemia patients with poor prognosis show high levels of T-helper 17 cells, while others with high T-helper1 cells had a good prognosis [23]. Th17 has an important role in autoimmune disorders as well as malignancies. However, the most updated data resulted in a controversial opinion about the role of Th17 in the pathogenesis of different cancers, such as CLL, AML, multiple myeloma, and non-Hodgkin lymphoma, while it was shown to have importance in disease prognosis in multiple myeloma (MM). Bartenhagen stated that IL-17 is a tumor-promoting factor in MM, because IL-17 level increases in MM and is accumulated in the bone marrow. Many microorganisms trigger the

transformation of B- lymphocytes, such as EBV, H. pylori, Plasmodium falciparum, HPV and HCV [24]. There is an indirect stimulation to immune responses by viruses, leading to abnormal proliferation of B- lymphocytes [25, 26]. Persistence of B cells causes lower symptoms but prolonged viremia exactly like EBV causes transformation. EBV was also reported to have an important role in increasing the risk of ALL in children [27]. During bone marrow transplantation, researchers found quiescent preleukemic cells that were thought to form residual cells [25]. Ample data from different articles stated the potential role of IL-17A in the immunobiology of leukemia [28,29]. The data from the present study agrees with that of Jain et.al who stated that serum concentrations of interleukin-17A in cases of different malignancies and cancerous tissues, ascites fluid of cancers patients, different kinds of tumors solid or blood malignancies such as CML, AML and CLL [10]. The function of IL-17 A may vary depending on the type, cause, and stage of cancer, with the potential role might be reflected during the initiation of certain tumors. IL-17A is the immune mechanism or defence mechanism to prevent the proliferation of B- lymphocyte clones, especially in the early clinical stages of leukemia [12]. The involvement of interleukins with different disorders has been proven by researchers previously [30-37]. Different Iraqi researchers stated the involvement of EBV and IL-17 in pathogenesis of many diseases [38-42]. We can conclude that EBV has a crucial role in the development of leukemia. EBV modulates the immune response leading to increase IL-17 secretion and the expression of its receptor, rendering them beneficial immune markers for the detection of leukemia.

4. Conclusions

The results of this study provide further evidence for the role of EBV in development and progression of leukemia. It also highlights the potential importance of IL-17 as an immune marker for the detection of leukemia. Further research is needed to fully understand the

mechanism by which EBV and IL-17 interact in leukemia and to identify new targets for the diagnosis and treatment of this disease.

Acknowledgment

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Table (1): Mean and ranges values of DNA viral load, IL-17 and IL-17R in CML patients and contro l groups. *p* values are also shown.

	Patients (mean)	Range	Control (mean)	Range	*p* value
DNA Viral load	31.7	27- 34.4	4.2	0.0-9.5	0.005
IL-17 (ng/ml)	113.87	46-350	15.4	7-23	0.001
IL- 17R (ng/ml)	180	90-400	6.81	2.2-10.34	0.0001

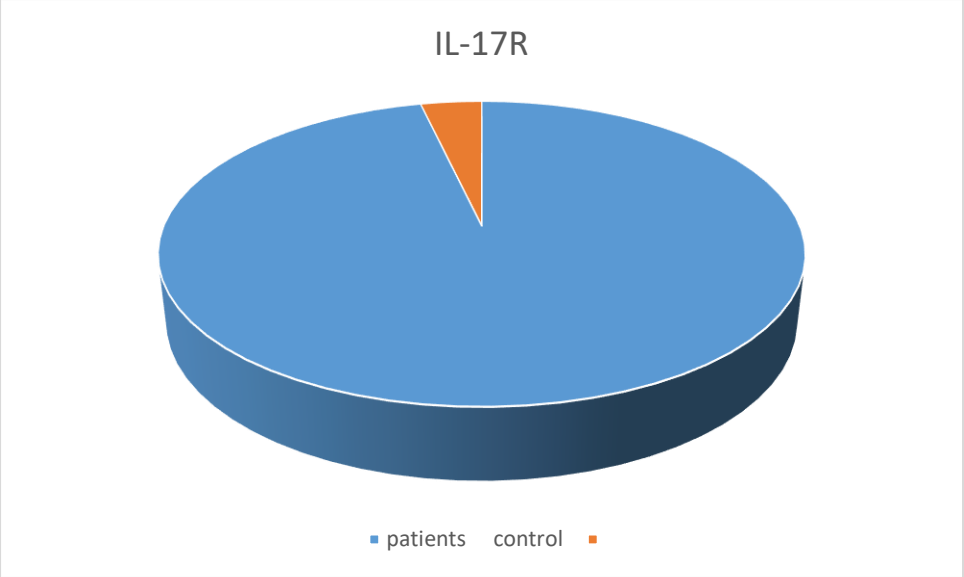

Figure (3): Comparison between CML patients and the control group according to IL-17R levels.

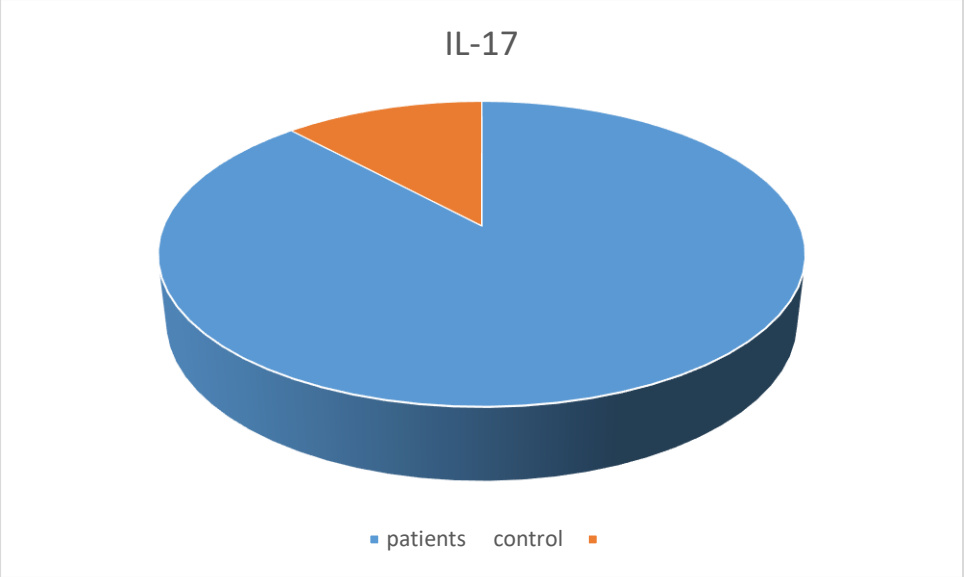

Figure (4): Comparison between CML patients and the control group according to IL-17 levels.

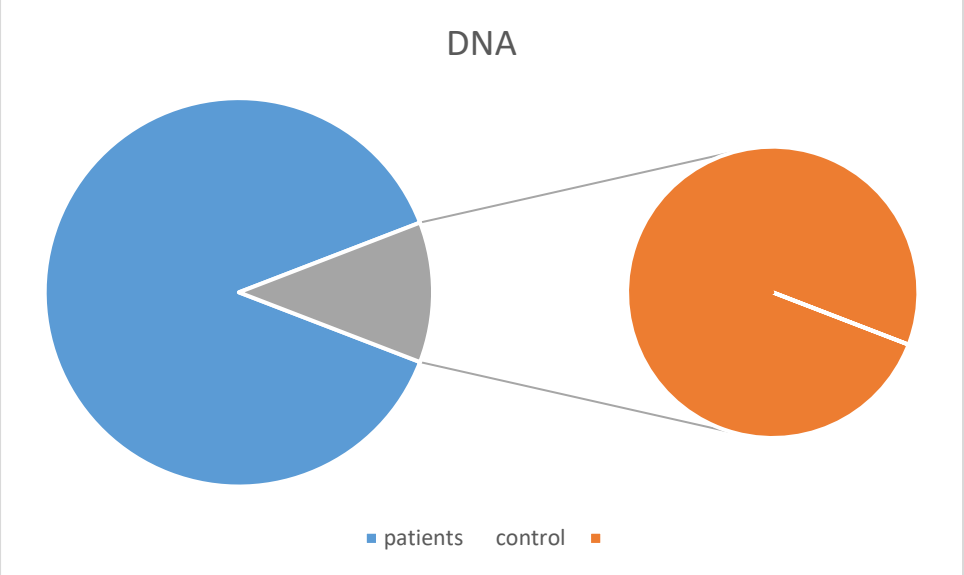

Figure (5): Comparison between CML patients and the control group according to DNA viral load.