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A Study Correlation between Levels IL-15, IL-23 and TNF-α in a Sample of Iraqi Psoriasis Patients

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Abstract

Psoriasis is defined as a series of events that begins in its initial stage with dermatitis and then progresses to more widespread inflammation and increased oxidative stress. The aim of this study was to determine whether psoriasis and the levels of IL-15, IL-23, and TNF-α are related, the ELISA technique was used to detect the levels of inflammation in psoriasis patients and to compare them with healthy individuals. This study included 150 samples, including 90 patients with psoriasis and 60 healthy individuals, and the study was conducted from November 2021 to April 2022. The current study revealed that there was a significant difference in the level of TNF-α in the group of psoriasis patients compared to its level in healthy individuals. Also, there was a significant increase in the level of IL-23 in psoriasis patients compared to its level in the healthy individuals, while there was no significant difference in the level of IL15 between the two groups. However, the statistical study showed a positive and highly significant correlation between IL-15 and IL-23 levels in psoriasis patients, as well as the same relationship between IL-15 and TNF-α levels, in addition to a significant correlation between IL-23 and TNF-α levels in the group of patients. This shows that there is a clear association between these interleukins and psoriasis and its association with the inflammatory status of psoriasis patients, although there was no increase in the level of interleukin-15, the association of interleukin-15 with other inflammatory indicators proves its involvement in psoriasis and an indirect effect on the inflammatory state of psoriasis.

Keywords: Psoriasis, IL-15, IL-23, TNF-α.

1. Introduction

Psoriasis is a widespread, chronic papulosquamous skin disease that affects people of all ages and causes significant harm to individuals and society [1]. It is one of the chronic autoimmune diseases affecting the skin of 0.6-4.8% of the world's population [2,3] Nearly 100 million people worldwide have psoriasis [4]. The disease often appears during the period of the second and fourth decades of life in patients with psoriasis [5] Psoriasis has been linked to a variety of behavioral

and systemic issues, including psoriatic arthritis, anxiety, depression, obesity, hypertension, diabetes mellitus, hyperlipidemia, metabolic syndrome, smoking, cardiovascular disease, alcoholism, Crohn's disease, lymphoma, and multiple sclerosis [6]. Most recent reports and research indicate that psoriasis is an abnormal proliferation of keratinocytes mediated by T lymphocytes [7].

IL-23 is primarily produced by antigen-presenting cells (APC), and its receptor is expressed by a wide range of innate and adaptive immune cells to enhance their functions [8]. External events like trauma or infection cause host cell-derived nucleotides to form a compound with antimicrobial peptides synthesized by keratinocytes. The plasmacyte dendritic cell produces type I interferons, which stimulate myeloid dendritic cells to secrete IL-23 and TNF-α [9]. According to recent research, activated T cells and DCs are essential to the pathogenesis of psoriasis, psoriasis is significantly brought on by the IL-23 production pathway, which shows that keratinocytes can create IL-23[10]. IL-23 may therefore play a major role in type 1 human autoimmune and inflammatory disorders [11].

Interleukin-15 is a pleiotropic cytokine of the 4-α-helix bundle cytokine family that includes not only cytokines such as IL-2, IL-3, IL-4, IL-6 and IL-21, but also growth factors like granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), erythropoietin and classical hormones, including human growth hormone and prolactin, [12].Interleukin-15 blood levels which are essential for regulating NK cell activity were also discovered to be similar in both psoriasis patients and healthy controls[13].

TNF-α is one of the most important cytokines involved in the inflammation that causes psoriasis, and high levels of TNF have been found in the blood of psoriasis patients in recent years. TNF is produced during the inflammatory response that causes psoriasis by the dysfunction of immune cells such as T cells, macrophages, activated keratinocytes, and dendritic cells. It is also produced directly from activated macrophages as well as from other cells. As for irregular production, it is the cause of different types of diseases [14, 15].

In addition, all of these cytokines stimulate psoriasis, so they were selected in this study [16, 17]. Several reports and research have also shown that the inflammatory response by tumor necrosis factor and other cytokines IL-23 that leads to the stimulation of angiogenesis and proliferation of keratinocytes, clearly contributes to the development of plaque psoriasis [18]. In addition, the results showed a positive relationship between TNF and disease severity [19]. This study aimed to analyses the association between the general inflammatory state of the body and its association with psoriasis in terms of these cytokines.

2. Materials and Methods

2.1. Controls and patients

This study included 90 patients with psoriasis between the ages of 11 and 73 years. All of these patients were from Al-Yarmouk Hospital located in the city of Baghdad, and 60 healthy individuals of the same age represented the control group, the samples were collected in a random way, where the number of males participating in this study was 73 and the number of females was 77, and samples were collected during a period between (November 2021 to April 2022).

2.2. Immune assays

Psoriasis patients and healthy individuals were studied in a case-control study to determine the levels of pro-inflammatory cytokines (IL-15, IL-23, and TNF-α) in psoriasis patients according to the manufacturer's protocol. The levels of each of these cytokines were estimated using an ELISA for each group of these cytokines. All from the same manufacturer, Bioassay Technology Laboratory

Venous blood was obtained using a sterile syringe. 6 ml of blood was drawn and then placed in a gel tube, and the tube was placed in a centrifuge at 2000–3000 rpm for 20 min. The serum was stored in 1.5 ml Eppendorf tubes and kept at −20 °C until all serological markers had been measured.

The ELISA plate was measured using a special device called ELISA reader with an absorbance of 450 nm to determine all concentrations of IL15, TNF-α and IL23 for each sample, each cytokine used had its absorbance according to the manufacturer's protocol of the kits.

2.3. Statistical analysis

The data were analysed using IBM SPSS V26 software. The results reported in this study were expressed as mean±SD **.**Levene's Test for Equality of Variances was used for IL15, IL 23, and TNF-α and the p-value were 0.126, 0.375, and 0.845 respectively, based on this result, parametric tests were used. Z-test was used to compare two proportions. Independent t-tests were used to test between study groups. Pearson correlation coefficient test was used to evaluate the linear relationship between two continuous variables using SPSS v.26, and if the categorical variable has two levels, a point-biserial correlation was used. Probability values less than 0.05 and 0.01 were considered significantly different [20].

3. Results and Discussion

This study was conducted on 150 Iraqi subjects (90 patients with psoriasis and 60 patients in healthy individuals (control groups). This study focused on a cytokine (TNF-α) and two interleukins (IL-23 and IL-15). A significant increase in the level of TNF-α was observed in the psoriasis patients group compared to its level in the healthy group and the P-value was (0.033*) (**Figure 1**). Also, there was a significant increase in the level of IL-23 in psoriasis patients compared to its level in the healthy individuals, and the P value was (0.001**) (**Figure 2**). While there was no significant difference in IL15 level between the two groups and the P-value was (0.201 N.S) (**Figure 3**).

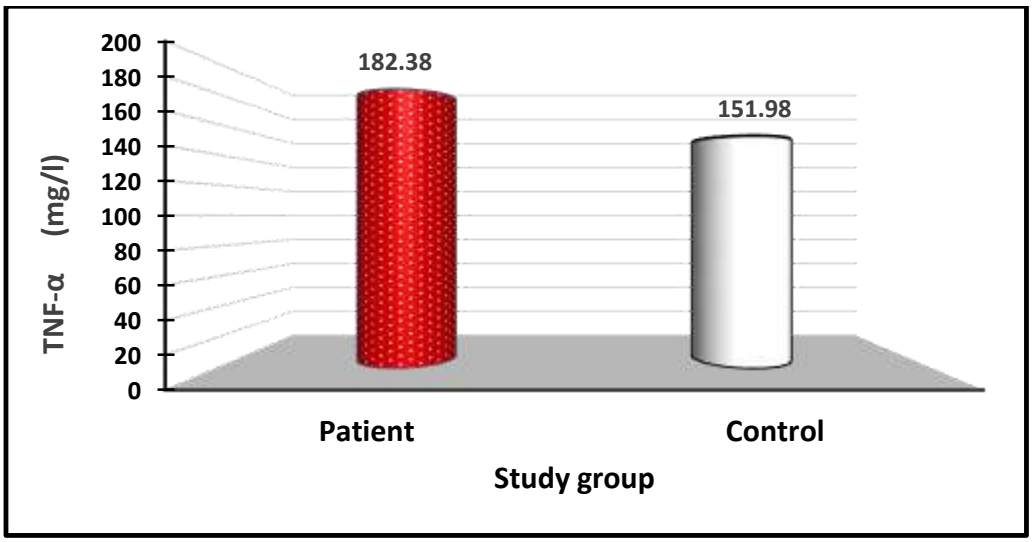

Figure 1. Serum level of TNF-α in Psoriasis patients compared to the control.

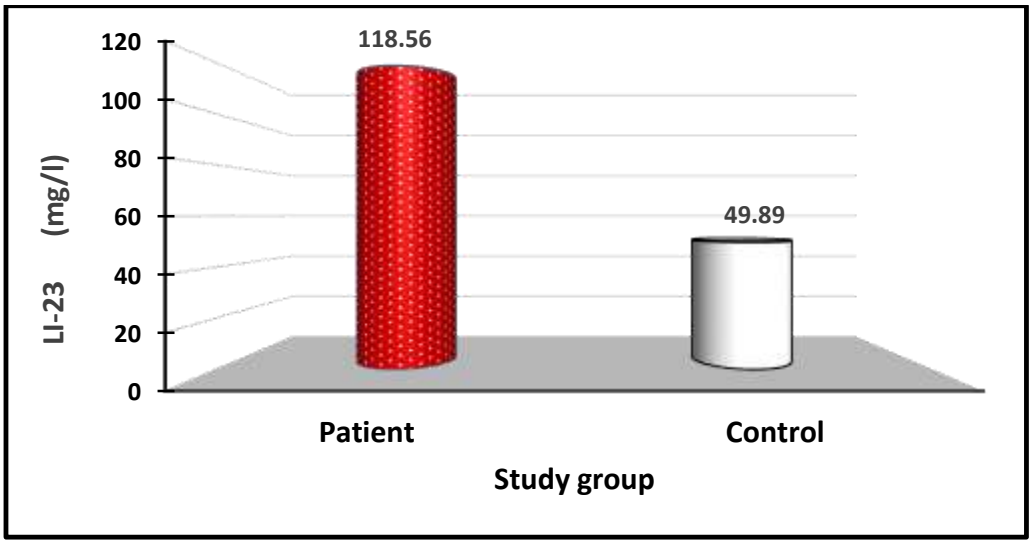

Figure 2. IL-23 serum levels in psoriasis patients and controls.

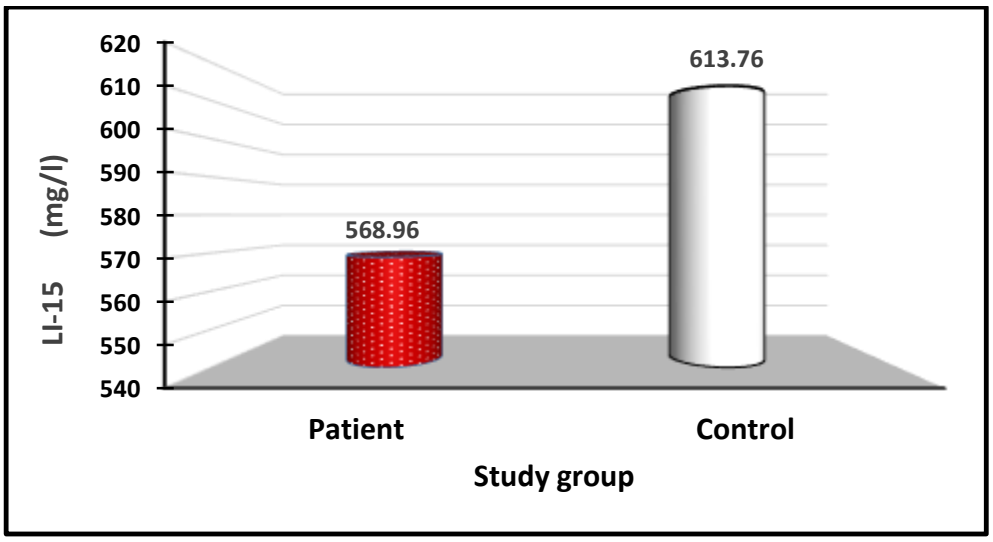

Figure 3. Serum level of IL-15(mg/l) in Psoriasis patients compared to the control**.**

TNF-α may lead to the enhancement of psoriasis by collaborating with other cytokines, according to theory, TNF-α is believed to be involved in the psoriasis development process [21]. In various studies, it was discovered that psoriatic patients' blood and lesional skin TNF-α levels were significantly greater than those of healthy controls. In addition, reducing the number of T cells and reducing epidermal hyperplasia in people with skin psoriasis using a specific drug as the improvement in the health status of patients with psoriasis was associated with a decrease in the level of TNF-α in the patients' blood [22, 23, 24]. In 2022, TNF inhibitors, especially etanercept, were used as a safe treatment for psoriasis in cases that were infected with HIV at the same time [25, 26]. Several reports and research have also demonstrated that the inflammatory response by TNF-α and other cytokines leads to the stimulation of angiogenesis and proliferation of keratinocytes, which contributes to the development of plaque psoriasis [27]. In addition, many types of research showed a positive correlation between TNF-α and disease severity (PASI) [28, 29, 30].

In recent research, it was proved that IL-23 is one of the most important cytokines in the world of the inflammatory process that leads to psoriasis, in addition to its importance in stimulating and activating Th-17, which in turn forms the psoriasis plaque [31,32]. The plasma level of IL-23 for patients with psoriasis Vulgaris was found to be higher when compared to the control group, and these results were consistent with many types of research and studies [33, 34, 35, 36, 37]. Likewise, IL-23 is one of the cytokines involved in the immune response to fungal and bacterial infections [38], The dysregulated production of IL-23 also stimulates autoimmune inflammation [39]. In some studies, they have targeted anti-TNF-α and IL-23 antibodies as an effective treatment for moderate to severe psoriasis patients [40]. This is evidence of its moral association with psoriasis.

IL-15 is an important cytokine in the activity of natural killer cells, but in our study, the level of IL15 did not show any change in psoriasis patients compared to control, Also, this statistical result was in agreement with other studies [41] [42] [43]. Interleukin-15 blood levels which are essential for regulating NK cell activity were also discovered to be similar in both psoriasis patients and healthy controls [45]. Also, a number of studies were conducted on patients suffering from Covid-19, and according to statistical studies, an increase in the level of IL-15 was found in the blood of patients, and this indicates an inflammatory cycle. Despite this, an increase in the level of IL-15 was not observed in patients with psoriasis.[46] It has also been demonstrated that IL-15 is a potentially relevant target in the IL-17 response in psoriasis. However, its mechanism is weak in humans and this may explain the lack of levels in the blood of patients with psoriasis [47]

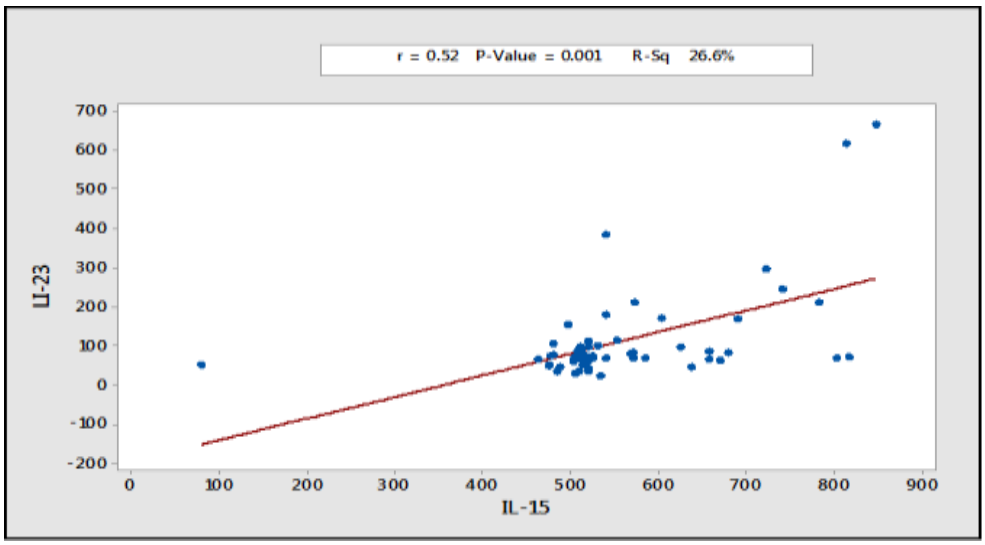

Figure 4: Correlation between serum levels of IL-23 and IL-15 in Psoriasis patients. (P < 0.01, r=0.52)

The statistical study showed a positive and strong significant correlation between the levels of IL-15 and IL-23 in patients with psoriasis, which means that the increase of one of them may lead to a rise in the other in this pathological condition (**Figure 4**). De Jesús-Gil et al is found that both IL-15 and L-23 are present in patients with psoriasis [48]. Also, the present results came in line with these previous studies. Where the results indicate the synergistic action of IL-15 and IL-23 selectively in cutaneous lymphocyte-associated antigen (CLA) positive (+) memory T cells in psoriasis [49], Some research has also indicated that IL-15 not only increased IL-23-expressing CD4+ T cells, but also enhanced antigen -specific IL-17 production, Synergistic with IL-23 this explains the positive correlation between these cytokines [50].

The same correlation was noted between the level of IL-15 and the TNF-α level, and a moderate positive significant correlation coefficient was found between them in the group of patients (**Figure 5**). Also, a significant correlation was strong between the level of IL-23 and TNF-α in the group of patients (**Figure 6**).

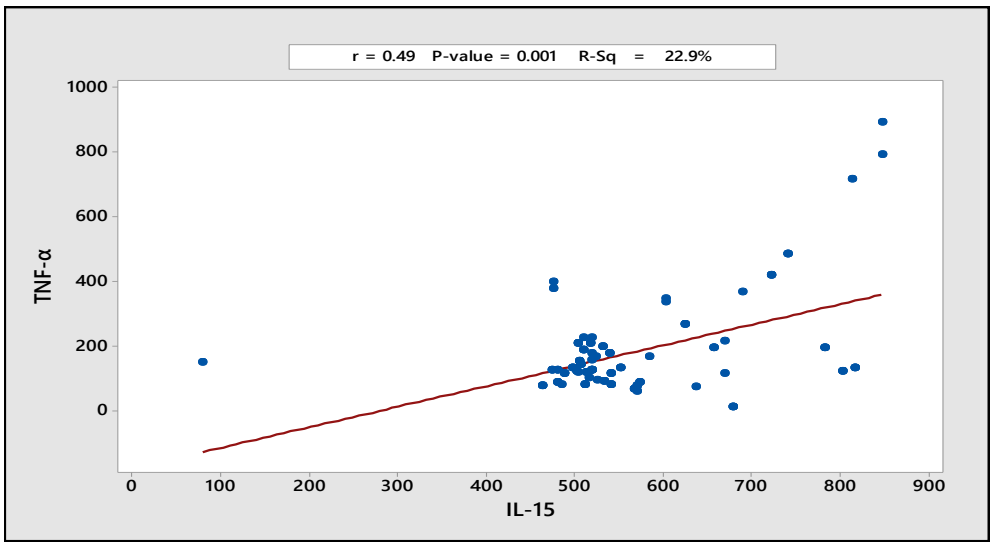

Figure 5. Correlation between serum levels of TNF-α and IL-15 in Psoriasis patients. (P < 0.01, r=0.49)

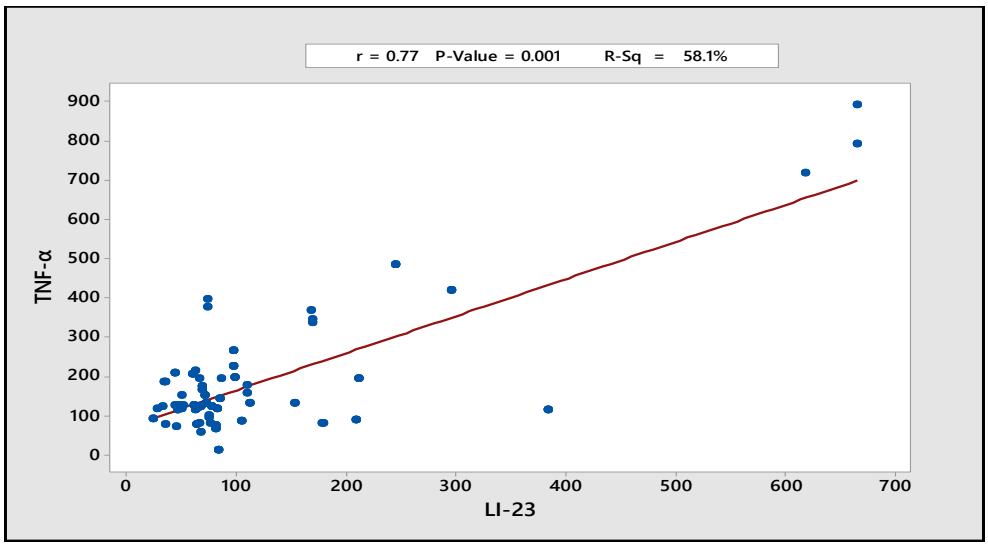

Figure 6: Correlation between serum levels of TNF-α and IL-23 in Psoriasis patients. ($P < 0.01$, $r=0.77$)

The reason for this correlation is that IL-15 facilitates the persistence of lymphocytes and also stimulates the production of certain inflammatory cytokines, one of which is TNF-α. In addition, dysregulated expression of IL-15 can lead to the development of autoimmune diseases [51]. the present results are in agreement with some previous studies previous studies. Also, Fraga et al. said that there is a linear relationship between IL-23 and TNF-α production by type 1 T cells [52], and this explains the significant correlation between IL-23 and TNF-α levels.

4. Conclusions

This indicates that there is a clear association between these interleukins (IL-15-IL-23-TNF-α) as well as there may be an association between the studied cytokines and indicates the rise in the level of cytokines in psoriasis and its control and its association with the inflammatory state of psoriasis patients although there is no There is an increase in the level of interleukin 15, but its association with other inflammatory indicators proves its involvement in psoriasis.

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Conflict of Interest

There are no conflicts of interest.

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Ethical Clearance

The samples were gained according to the University of Baghdad, College of Sciences, Ethics Approval Committee.

References

1. Naldi, L. Epidemiology of psoriasis: current drug targets. *Inflamm. Allergy*, **2004**; *3*, 2, 121–128.
2. Numerof, R.P.; Asadullah, K. Cytokine and anti-cytokine therapies for psoriasis and atopic dermatitis. *J. Bio. Drugs*, **2006**; *20*, 2,93-103.
3. Guðjónsson, J. E.; Valdimarsson, H.; Kárason, A.; Antonsdóttir, A. A.; Rúnarsdóttir, E. H.;Gulcher, J.R.; Stefánsson, K HLA-Cw6-positive and HLA-Cw6-negative patients with psoriasis vulgaris have distinct clinical features. *J. Investig. Dermatol.* **2002**, *118*, 2, 362-365 .
4. World Heath Organization, Global Report in Psoriasis, **2016**.
5. Kuba, R.H.; Al-Qadhi, B.N.; Fadheel, B.M.; Effect of the Biological Drug Etanercept on Tumor necrosis factor-α Levels in Psoriatic Patients. *Iraqi J. Sci.,* **2018**, *59*, 2, 998–1005.
6. Guenther, L.; Gulliver, W. Psoriasis comorbidities. *J. Cutan. Med. Surg.* **2009**; *13*, 5,77-87.
7. Iqbal, M.N. Levels of interleukins 6 and 8 in Psoriatic patients serum. *Ibn AL-Haitham J. Pure Appl. Sci.*, **2017**, *23*, 3, 15-24.
8. Abdul-Hussein, S.S.; Ali, E.N.; Alkhalidi, N.M.F.; Zaki, N.H.; Ad'hiah, A.H. Roles of IL-17A and IL-23 in the Pathogenesis of Ulcerative Colitis and Crohn's Disease. *Iraqi J. Sci*., **2021**; *62*, 8, 2526–2535.
9. Lande, R.; Gregorio, J.; Facchinetti, V.; Chatterjee, B.; Wang, Y.H.; Homey, B.; Gilliet, M. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. *J. Nat.*, **2007**; *449*, 7162, 564-569.
10. Kauffman, C.L.; Aria, N., Toichi, E.; McCormick, T.S.; Cooper, K.D.; Gottlieb, A.B.; Mascelli, M.A.; A phase I study evaluating the safety, pharmacokinetics, and clinical response of a human IL-12 p40 antibody in subjects with plaque psoriasis. *J. Investig. Dermatol*., **2004**; *123*, 6, 1037-1044.
11. Pietrzak, A.T.; Zalewska, A.; Chodorowska, G.; Krasowska, D.; Michalak-Stoma, A.; Nockowski, P.; Roliński, J.M. Cytokines and anticytokines in psoriasis. *J. Clin. Chimica Acta*, **2008**; 394, 1-2, 7-21.
12. Budagian, V.; Bulanova, E.; Paus, R.; Bulfone-Paus, S. IL-15/IL-15 receptor biology: a guided tour through an expanding universe. *J. Cytokine Growth Factor Rev*., **2006**; *17*, 4, 259-280.
13. Dunphy, S.E.; Sweeney, C.M.; Kelly, G.; Tobin, A.M.; Kirby, B.; Gardiner, C.M. Natural killer cells from psoriasis vulgaris patients have reduced levels of cytotoxicity associated degranulation and cytokine production. *J. Clin. Immunol*., **2015;** *177*, 43-49.
14. Majeed, I.A.; Al-Shawi, N.N. Effects of Omega-3 Co-Administered with Therapeutic Dose of lornoxicam on Male Rats' Liver. *Iraqi j. Pharmac. Sci.*, **2019**; 28, 2, 159-164.
15. Arican, O.; Aral. M.; Sasmaz, S.; Ciragil P.; Serum levels of TNF-α, IFN-γ, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *J. Med. Inflamm*., **2005**; *5*, 273-279.
16. Liu. T.; Li, S.; Ying, S. The IL-23/IL-17 pathway in inflammatory skin diseases: from bench to bedside. *J. Front Immunol.*, **2020**; *11*, 59475.
17. Kuchař, M.; Vaňková, L.; Petroková, H.; Cerný, J.; Osička, R.; Pelák, O.; Sípová, H.; Schneider, B.; Homola, J.; Sebo, P.; Kalina, T.; Malý, P. Human interleukin-23 receptor antagonists derived from an albumin-binding domain scaffold inhibit IL-23-dependent ex vivo expansion of IL-17-producing T-cells. *J. Proteins Struct. Func. Bioinform*., **2014**; *82*, 6, 975-989.

18. Myers, B.; Thibodeaux, Q.; Reddy, V. Biologic treatment of 4 HIV-positive patients: a case series and literature review. *J. Psoriasis Psoriatic Arthritis*, **2021**; *6*, 1, 19–26.
19. Abanmi, A.; Al Harthi, F.; Al-Agla. R. Serum levels of proinflammatory cytokines in psoriasis patients from Saudi Arabia. *Int. J. Dermatol*., **2005**; *44*, 1, 82-83.
20. Daniel. W.W.; Cross, C.L. *Biostatistics, A Foundation for analysis in the health sciences*. Journal of John Wiely and Sons **2013**; 958.
21. Yost, J.; Gudjonsson, J.E. *The role of TNF inhibitors in psoriasis therapy*. New implications for associated comorbidities **2009**; F1000 medicine reports 1.
22. Mizutani, H.; Ohmoto, Y.; Mizutani, T.; Murata, M.; Shimizu, M. Role of increased production of monocytes TNF-α, IL-1β and IL-6 in psoriasis: relation to focal infection, disease activity and responses to treatments. *J. Dermatol. Sci*. **1997**; *14*, 2,145-153.
23. Uyemura, K.; Yamamura, M.; Fivenson, D.F.; Modlin, R.L.; Nickoloff, B.J; The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type 1 cell-mediated response. *J. Investig. Dermatol*., **1993**; *101*, 5,701-705.
24. De Rie, M.A.; Goedkoop, A.Y.; Bos, J.D. Overview of psoriasis. *J. Dermatol. Therapy*, **2004**; *17*, 5, 341-349.
25. Hong, J.J.; Hadeler, E.K.; Mosca, M.L.; Brownstone, N.D.; Bhutani, T. Liao, W.J. TNF-alpha inhibitors and ustekinumab for the treatment of psoriasis: therapeutic utility in the era of IL-17 and IL-23 Inhibitors. *J. Psoriasis Psoriatic Arthritis*, **2022**; *7*, 2, 79-92.
26. Domm. S.; Cinatl. J.; Mrowietz. U.; The impact of treatment with tumour necrosis factor-alpha antagonists on the course of chronic viral infections: a review of the literature. *Br. J. Dermatol*., **2008**; *159*, 6, 1217–1228.
27. Myers, B.; Thibodeaux, Q.; Reddy. V. Biologic Treatment of 4 HIV-Positive Patients: A Case Series and Literature Review. *J. Psoriasis Psoriatic Arthritis*, **2021**; 6, 1, 19–26.
28. Arican, O.; Aral, M.; Sasmaz, S.; Ciragil, P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *J. Mediators Inflamm*., **2005**; *2005*, 5, 273–279.
29. Abanmi, A.; Al-Harthi, F.; Al-Agla, R. Serum levels of proinflammatory cytokines in psoriasis patients from Saudi Arabia. *Int. J. Dermatol*., **2005**; *44*, 1, 82–83.
30. Roussaki-Schulze. AV.; Kouskoukis. C.; Petinaki. E. Evaluation of cytokine serum levels in patients with plaque-type psoriasis. *Int. J. Clin. Pharmacol. Res*., **2005**; *25*, 4, 169–73.
31. Fotiadou, C.; Lazaridou, E.; Sotiriou, E.; Ioannides, D. Targeting IL-23 in psoriasis: current perspectives. J. *Psoriasis (Auckl)*, **2018**; 8, 1, 1-5.
32. Dattola, A.; Silvestri, M.; Tamburi, F.; Amoruso, G. F.; Bennardo, L.; Nisticò. S.P. Emerging role of anti-IL23 in the treatment of psoriasis: When humanized is very promising. *J. Dermatologic Therapy* **2020**; *33*, 6, 14504
33. Wolk, K.; Witte, E.; Wallace, E.; Döcke, W.D.; Kunz, S.; Asadullah, K.; Volk, H.D.; Sterry, W.; Sabat, R. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. *Europ. J. Immunol*., **2006**; *36*, 5, 1309-1323.
34. Takahashi, H.; Tsuji, H.; Hashimoto, Y.; Ishida-Yamamoto, A.; Iizuka, H. Serum cytokines and growth factor levels in Japanese patients with psoriasis. *Clin. Exper. Dermatol, Exper. Dermatol*., **2010**; *35*, 6, 645-649.
35. Vähävihu, K.; Ala-Houhala, M.; Peric, M.; Karisola, P.; Kautiainen, H.; Hasan, T.; Snellman, E.; Alenius, H.; Schauber, J.; Reunala, T. Narrowband ultraviolet B treatment improves

vitamin D balance and alters antimicrobial peptide expression in skin lesions of psoriasis and atopic dermatitis. *Br. J. Dermatol*., **2010**; *163*, 2, 321-328.

36. Coimbra, S.; Oliveira, H.; Reis, F.; Belo, L.; Rocha, S.; Quintanilha, A.; Santos-Silva. A. Interleukin (IL)-22, IL-17, IL-23, IL-8, vascular endothelial growth factor and tumour necrosis factor-α levels in patients with psoriasis before, during and after psoralen–ultraviolet A and narrowband ultraviolet B therapy. *Br. J. Dermatology* **2010**,*163*, 6, 1282-1290.
37. Girolomoni, G.; Strohal, R.; Puig, L.; Bachelez, H.; Barker, J.; Boehncke, W.H.; Prinz J. C. The role of IL-23 and the IL-23/TH 17 immune axis in the pathogenesis and treatment of psoriasis. *J. Europ. Acad. Dermatol. Venereol.*, **2017**; *31*, 10, 1616-1626.
38. Curtis. M.M.; Way. S.S.; Interleukin-17 in host defence against bacterial, mycobacterial and fungal pathogens. *J. Immunol.* **2009**; *126*, 177-185.
39. Langrish, C.L.; Chen, Y.; Blumenschein, W.M.; Mattson, J.; Basham, B.; Sedgwick, J.D.; McClanahan, T.; Kastelein, R.A.; Cua, D. J. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J. Exper. Med*., **2005**; *201*, 2, 233-240.
40. Dapavo, P.; Siliquini, N.; Mastorino, L.; Avallone, G.; Merli, M.; Agostini, A.; Ribero S; Efficacy, safety, and drug survival of IL-23, IL-17, and TNF-alpha inhibitors for psoriasis treatment: a retrospective study. *J. Dermatol. Treat.* **2022**; *33*, 4, 2352-2357.
41. Dunphy, S.E.; Sweeney, C.M.; Kelly, G.; Tobin, A.M.; Kirby, B.; Gardiner, C.M. Natural killer cells from psoriasis vulgaris patients have reduced levels of cytotoxicity associated degranulation and cytokine production. *J. Clin. Immunol.,* **2017**; *177*, 43-49.
42. Tassiulas, I.; Duncan, S.R.; Centola, M.; Theofilopoulos, A.N.; Boumpas, D.T. Clonal characteristics of T cell infiltrates in skin and synovium of patients with psoriatic arthritis. *J. Human Immunol*., **1999**; *60*, 6, 479-491.
43. Danning, C.L.; Illei, G.G.; Hitchon, C.; Greer, M.R.; Boumpas, D. T.; McInnes, I.B; Macrophage-derived cytokine and nuclear factor κB p65 expression in synovial membrane and skin of patients with psoriatic arthritis. *Arthritis Rheumat. Official J. Am. Coll. Rheumatol*., **2000**, *43*, 6, 1244-1256.
44. Dunphy, S.E.; Sweeney, C.M.; Kelly, G.; Tobin, A.M.; Kirby, B.; Gardiner C.M. Natural killer cells from psoriasis vulgaris patients have reduced levels of cytotoxicity associated degranulation and cytokine production. *J. Clin. Immunol*., **2017**; *177*, 43-49.
45. Kalinina, O.; Golovkin, A.; Zaikova, E.; Aquino, A.; Bezrukikh, V.; Melnik, O.; Shlyakhto, E. Cytokine Storm Signature in Patients with Moderate and Severe COVID-19. *Int. J. Mol. Sci*., **2022**; 23, 16, 8879.
46. McInnes. I.B.; Liew. F.Y. Interleukin 15: a proinflammatory role in rheumatoid arthritis synovitis. *J. Immunol. Today*, **1998**; 19, 2, 75-79.
47. de Jesús-Gil, C.; Ruiz-Romeu, E.; Ferran, M.; Sagristà, M.; Chiriac, A.; García, P.; Santamaria-Babí, L.F. IL-15 and IL-23 synergize to trigger Th17 response by CLA+ T cells in psoriasis. *Exper. Dermatol*., **2020**; *29*, 7, 630-638.
48. Yoshihara, K.; Yamada, H.; Hori, A.; Yajima, T.; Kubo, C.; Yoshikai, Y. IL-15 exacerbates collagen-induced arthritis with an enhanced CD4+ T cell response to produce IL-17. *Europ. J. Immunol*., **2007**; *37*, 10, 2744-2752.
49. de Jesús-Gil, C.; Ruiz-Romeu, E.; Ferran, M.; Sagristà, M.; Chiriac, A.; García, P,; Santamaria-Babí, L.F. IL-15 and IL-23 synergize to trigger Th17 response by CLA+ T cells in psoriasis. *J. Exper. Dermatol*., **2020**; *29*, 7, 630-638.

50. Celis, R.; Planell, N.; Fernández-Sueiro, J.L.; Sanmartí, R.; Ramírez, J.; González-Álvaro, I.; Cañete, J.D; Synovial cytokine expression in psoriatic arthritis and associations with lymphoid neogenesis and clinical features. *J. Arthritis Res. Therapy*, **2012**; *14*, 2, 1-9.
51. Waldmann, T.A. Targeting the interleukin-15/interleukin-15 receptor system in inflammatory autoimmune diseases. *Arthritis Res. Ther*, **2004**; *6*, 4,174–177.
52. Fraga, N.A.D.A.; Oliveira, M.D.F.P.D.; Follador, I.; Rocha, B.D.O.; Rêgo, V.R. Psoriasis and uveitis: a literature review. *J. Anais brasileiros de dermatologia***, 2012**; *87*, 877-883.