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Immunological study on some of Psoriatic Iraqi PatientsTreated with Etanercept

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Abstract:-

The present study is accomplished on (60) patients and (30) healthy individual. Serum levels of (Interleukin 17A (IL17A), Interleukin 17AR (IL17AR)and anticitrullinated protein antibody(ANTI-CCP) is estimated using Enzyme Linked Immunosorbent Assay (ELISA) technique and RF by latex test. Our results were high starting with IL17A mean value before treatment (967.24±784.1), IL17AR (818.62±647.33),ANTI-CCP (33.96±51.82) and with P value of (<0.0001). These levels were reduced significantly after treatment with (Etanercept) injection to give a mean levels of IL17A (360.61±302.38), IL17AR (118.67±191.85), ANTI-CCP (33.98±38.04) and with P value of (<0.0001).Patients were diagnosed with psoriasis arthritis (PsA) by calculating the degree of ANTI-CCP and results were 12 patients before treatment and 17 patients after treatment.ANTI-CCPwas important to diagnose PsA. IL17A, IL17AR have an important role in increasing the inflammation and as a marker for follow up after choosing a treatment in psoriasis and PsA.

Keywords: - *Psoriasis, IL17A, IL17AR, Anti-CCP, RF.*

I. Introduction:-

Psoriasis is a common skin condition which speeds up the skin cells' life cycle. Bring in the rapid deposition of cells on the skin surface. Additional skin cells develop scales and itchy and occasionally painful red spots. Psoriasis is a chronic condition that sometimes comes and goes. The aim of treatment is to stop the cells from growing too quickly. Psoriasis is cureless but it can control symptoms. Measures to lifestyle such as exercise, avoidance of smoking and stress reduction may help. Symptoms and symptoms of psoriasis differ for everyone. Common symptoms and signs include: Red patches of skin covered with thick, silvery scales, Tiny scaling spots (commonly seen in children), Dry broken skin that may bleed, itch, burn or soreness, Thickened, bruised or ridged nails, Swollen and rigid joints [1]. Psoriasis affects the skin and hair, and a variety of co-morbidities. Localized or generalized skin lesions are often symmetrical, strongly demarcated, red papules and plaques and are typically covered with white or silver scales. Lesions

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give rise to scratching, stinging and discomfort. About 1.3% and 34.7% [1] of psoriasis patients experience chronic, inflammatory arthritis (psoriatic arthritis), which contributes to joint deformations and impairment. Nail changes grow between 4.2 per cent and 69 per cent of all patients with psoriasis [2]. It is stated that individuals with psoriasis are at elevated risk of developing other severe health conditions, such as cardiovascular and other non-communicable diseases (NCDs). Psoriasis is responsible for a great physical, emotional and social burden [3].

Another type of psoriasis isPsoriatic arthritis was first described in 1973 by Moll and Wright as "an inflammatory arthritis associated with psoriasis that typically presented with a negative serological test for rheumatoid arthritis[4] Five clinical characteristics of psoriatic arthritis were used for classification: distal arthritis, asymmetric oligoarthritis, symmetric polyarthritis, arthritis with psoriatic arthritis .

This classification scheme is most important early in the course of the disease and as the disease progresses the subtype of psoriatic arthritis may change. The most frequently affected joints are the spine and the inter-phalangeal distal (DIP) joints[5], each affecting 40–50 per cent of cases. Spinal arthritis most often occurs in many joints after many years of illness. The most specific manifestations of psoriatic arthritis are distal arthritis and arthritis mutilans. Psoriasis is commonly associated with various comorbidities, including psoriatic arthritis and cardiometabolic disorders such as obesity, hypertension, diabetes, and metabolic syndrome [6].

Evidence has accumulated that interleukin (IL)-17-producing T-cells (Th17) play an essential role in psoriasis pathogenesis. IL-17 was described as a psoriasis 'horse' cytokine and represents an important therapeutic goal. IL-17 has also been recognized as a significant risk cytokine for atherosclerosis and that decreased expression or inhibition of IL-17 results in a decrease in the development of atherosclerotic lesions [7].

The cytokine family IL-17 consists of six cytokines (IL-17A – IL-17F) and five (IL-17RA – IL-17RE) receptors[8]. Of these, only levels of IL-17A, IL-17C, and IL-17F mRNA from patients with psoriasis are elevated in lesional skin and these cytokines have been shown to induce expression of proinflammatory target genes in keratinocytes. The heterodimer ligands IL-17A, IL-17F, and IL-17 A/F act through an IL-17RA/RC complex, and IL-17C acts through an IL-17RA/RE complex, with anti-IL-17RA Abs capable of blocking all four ligand complexes' activities [9].

In addition to RF, antibodies against cyclic citrullinated peptide (anti-CCP) have been a highly sensitive method for RA diagnosis for years, and have been shown to be associated with higher disease activity and more erosive progression. Their prevalence in RA tends to increase when associated with RF, while patients with RF-negative RA display an incidence of anti-CCP between 20 percent and 60 percent [10].

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II. Materials and Methods:-

Subject:

A case-control study was performed in which Iraqi psoriatic patients and controls were investigated to estimate the levels of one major pro-inflammatory cytokine (IL17A, IL17AR, ANTI-CCP and RF) in the serum of psoriatic patients and a healthy subject using enzyme / associated immunosorbent assay (ELISA commercial kit) in the manufacturing instruction.

Patient:

Sixty patients with psoriasis clinically determined[15] were enrolled in a dermatological clinic at Al-Kindi Hospital between the periods of December to July.

Controls:

Thirty control included in this work (male: 13-female; 17) which they were healthy individual.

Collection of Specimens:

Venous blood was collected with 3 ml sterile syringe, a gel tube was filled with 3 ml of blood and after clot formation, the tube was centrifuged 4000 rpm for fifteen minutes. The serum was stored in 1.5 ml Eppendorf tubes and frozen to -20 º c until all the serum tests measured. The tube was then frozen at -20 º c.

Assessment of interleukin-17A Serum Levels:

The principle behind this ELISA kit is that it uses the ELISA Sandwich, the microplates in the package were coated previously with a human IL-17A-specific antibody.

Assay Procedure: Elabscience [12]

The compounds of this kit were warmed at (19-25 Cº) before accomplish the procedure then the below steps were carried:

1. The first step was adding 100 microliters of working solution to the columns, and also applicated on the specimens, then covering the plate with foil paper that provide in the kits and was incubated at 37 Cº for ninety min.

2. The liquid was drained from each well. Every well was immediately supplied with one hundred microliters biotinylated detection. Next, the plate was coated and gently mixed and then at (37 ° C) for 1 hour the incubation was held.

3. The sol. was decanted by Wells, 350 microliters of washing solution buffer to all well was added. And they were drenched for two minutes to each well, the sol. was aspired or decanted and patted with absorbent paper to dry.

4. Each well was supplemented with one hundred microliters of HRP conjugate working sol. then coated with plate sealer. And for thirty minutes that they were already incubated at "37 ° C".

5. All wells were decanted from the solution; approximately ninety micro liters of the substrate's reagent were applied, and coated with "sealing plate", and after that incubation step at (37 ° C) for about fifteen min.

6. For termination of the test fifty microliters of stop solution were added, then absorbance was determined at 450 nm.

Interleukin 17 Receptor A (IL17RA), ELISA Kit:

The microtiter plate provided for in this package was pre-coated with an IL17RA-specific antibody. Standards or specimens are then added with an IL17RA-specific biotin-conjugated antibody to the respective microtiter plate wells.

Assay Procedure: Elabscience [13]

1. Normal identification of wells, blanks and specimens with diluents. One of them was clean. Seven wells were prepared. Hundred µL have been applied to each of the normal dilutions, one blank and specimens in the correct wells. Plate was then incubated with a sealer and measured for 2 hours.

2. The liquid has been drained from every well; do not wash.

3. A working solution was applied to each well by hundred µL of detection reagent and was Incubate at 37oC for 1 hour after being covered with a plate sealer.

4. Using a spray bottle, multi-channel pipette, multi-purpose dispenser or automatic washing machine, the solution was aspirated and washed with a three hundred and fifty µL 1 x 1 wash solution per well, and was allowed to sit for a minute or two. Residual liquid was completely drained from all wells by picking up the plate on the absorbent surface, and was completely washed 3 times. Any separate washing machine was removed by suction or casting after the last wash. The plate turned toward the absorbent surface.

5. Every well was supplemented with a hundred µL of B working reagent detection solution. Incubate at 37 ° C for 30 minutes, after a plate sealer has been sealed.

6. The suction was repeated 5 times / Step 4.

7. A ninety µL of substrate solution was applied to each well and covered with a new sealer pad, then incubated at 37 ° C (not to exceed 30 minutes) for 15-25 minutes. It was shielded from light, then liquid turned blue after the solution was applied to the substratum.

8. Each well had a fifty µL stop solution applied. After the solution was applied, the liquid turned yellow and mixed the liquid by clicking on the side of the bottle.

9. Every drop of water and fingerprints was hidden below the plate and it was made sure there was no bubble on the liquid surface. The microplate reader was then turned on and the calculation was performed at 450 nm.

Human CCP-Ab(anticyclic citrullinated peptide) ELISA Kit:

The form used in this ELISA package is Sandwich-ELISA. The micro ELISA plate contained in this kit is pre-coated with a Human CCP-Ab specific antigen.

Assay Procedure: Elabscience [14]

1. The standard working solution was added to the first two columns each solution concentration was added repeatedly, to one well, side by side (100μL per well). Specimens were added to other wells (100μL per well). The plate covered with the seal in the set, and then plate was incubated for 90 minutes at 37 ℃.

2. The liquid was removed, without washing, from each well. 100 μL of Ag Biological Discovery Solution was then immediately applied to each well. The plate was sealer coated and combined, and was eventually incubated at 37 ° C for 1 hour.

3. The solution was aspirate poured from each well (350 μL of wash buffer was applied to each well, soaking it from each well for 1 minute), then drying it against a clean absorbent surface. Repeated this move 3 times.

4. Each well was dissolved by adding hundred μL of HRP Conjugate. And was coated with sealer plate, incubated at 37 ° C for 30 minutes.

5. Then each well aspired the solution, the washing process for was repeated five times.

6. Ninety μL of substratum reagent was applied to each well, covered with a new sealer plate, then incubated at 37 ° C for 15 minutes, the plate protected against light.

7. Fifty μL of stop solution was added to each well.

8. The plate was read at 450 nm.

9. The results were calculated.

Results:-

Table 1 studied parameter of patients before treatment depending on age.

Parameters	Age ranging				P value
	10-24 years n=7	25-39 years n=10	40-54 years n=9	55-70 years n=4	

IL-17A	992.46±576.20	1260±1053.64	530±343.43	1175±846.06	<0.0001
IL-17AR	864.08±590.69	971±791.30	463.33±236.80	1157.5±843.10	<0.0001
ANTI-CCP	17.85±9.36	53±73.37	34±52.20	14.5±7.14	0.206

As shown in Table 1, psoriasis mostly affects at the age of 25 to 55 and is average until the end of middle age, no significant change in P values of IL-17A and IL-17AR. There a significant change between IL17A and all age's groups with P value (< 0.0001), another significant change is with IL17AR with P value (< 0.0001).

Table 2: The studied parameter of patients after treatment depending on age.

Parameters	Age ranging				P value
	10-24 years n=5	25-39 years n=13	40-54 years n=10	55-70 years n=2	
IL-17A	454.82±451.94	364.50±288.02	268.08±164.84	562.5±618.72	<0.0001
IL-17AR	64.54±88.47	89.92±180	159.01±226.59	239.2±338.28	<0.0001
ANTI-CCP	36.22±21.30	30.52±34.64	34.15±47.21	50±70.71	<0.0001

Table 2 results which is after treatment, p value levels are similar to these results of both before and after treatments, there is a significant change with all parameters IL17A, IL17AR AND ANTI-CCP P value at a different aging range are all (<0.0001)

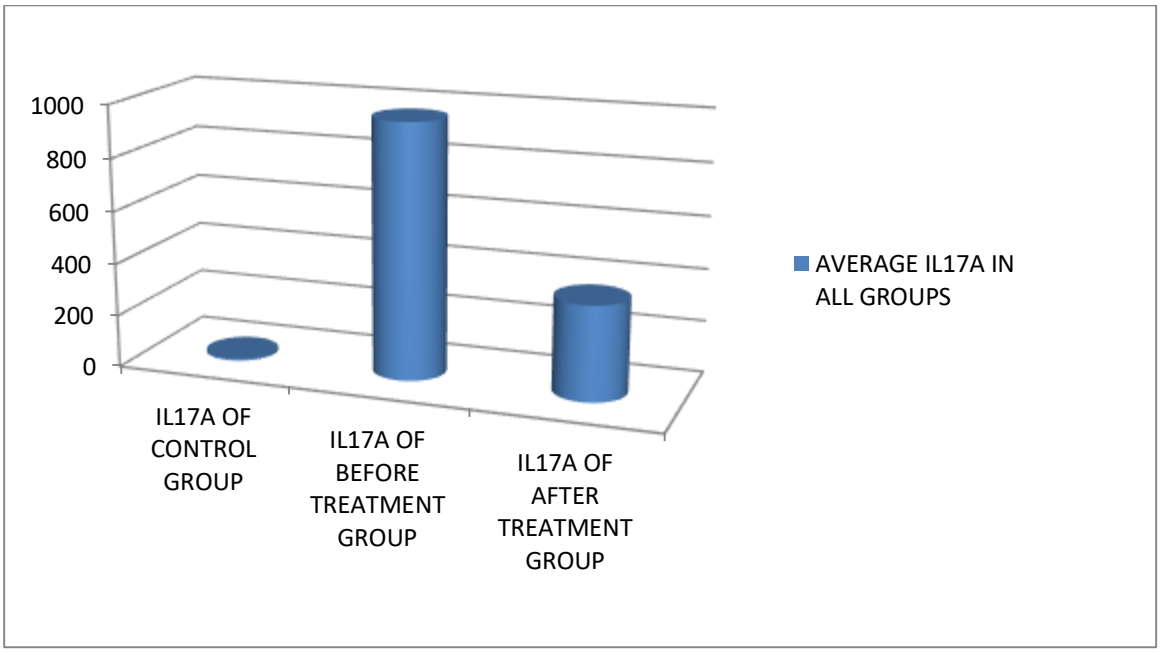

Figure 1 Average levels of control, before and after treatment groups of IL17A

Normal group have serum levels of IL17A while patients with psoriasis have high levels of IL17A and it was significantly reduced after treatment.

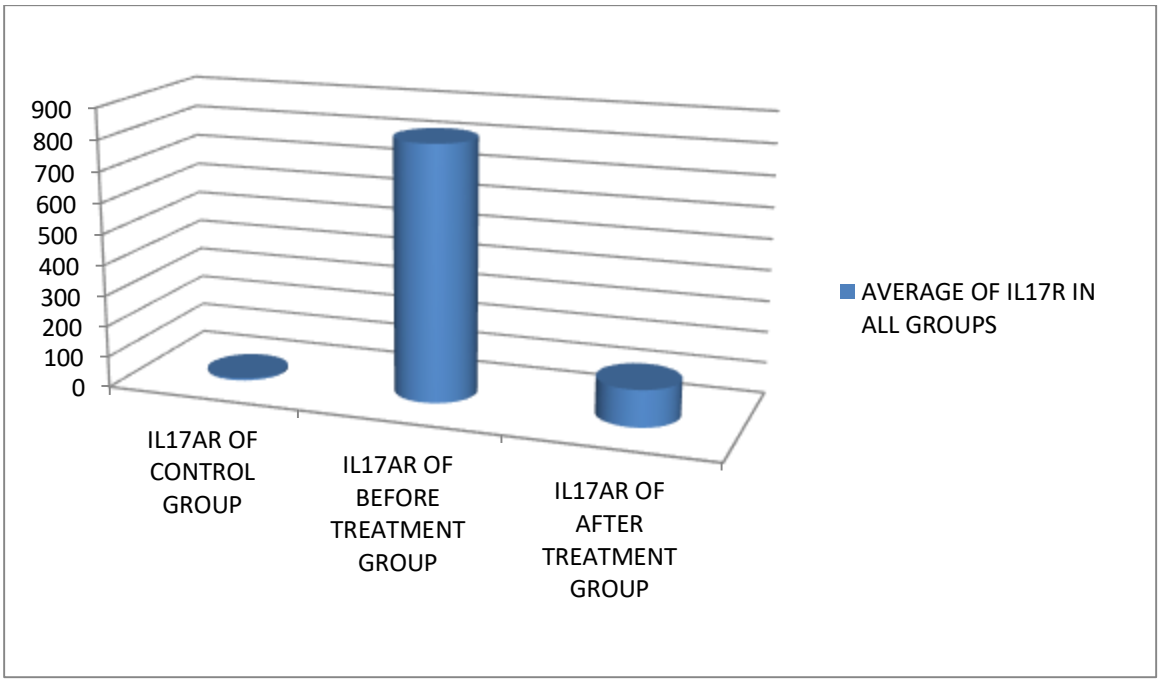

Figure 2 Average levels of control, before and after treatment groups of IL17AR

Serum levels of IL17AR are normal with control groups yet it is high with patients with psoriasis and it was greatly reduced after treatment.

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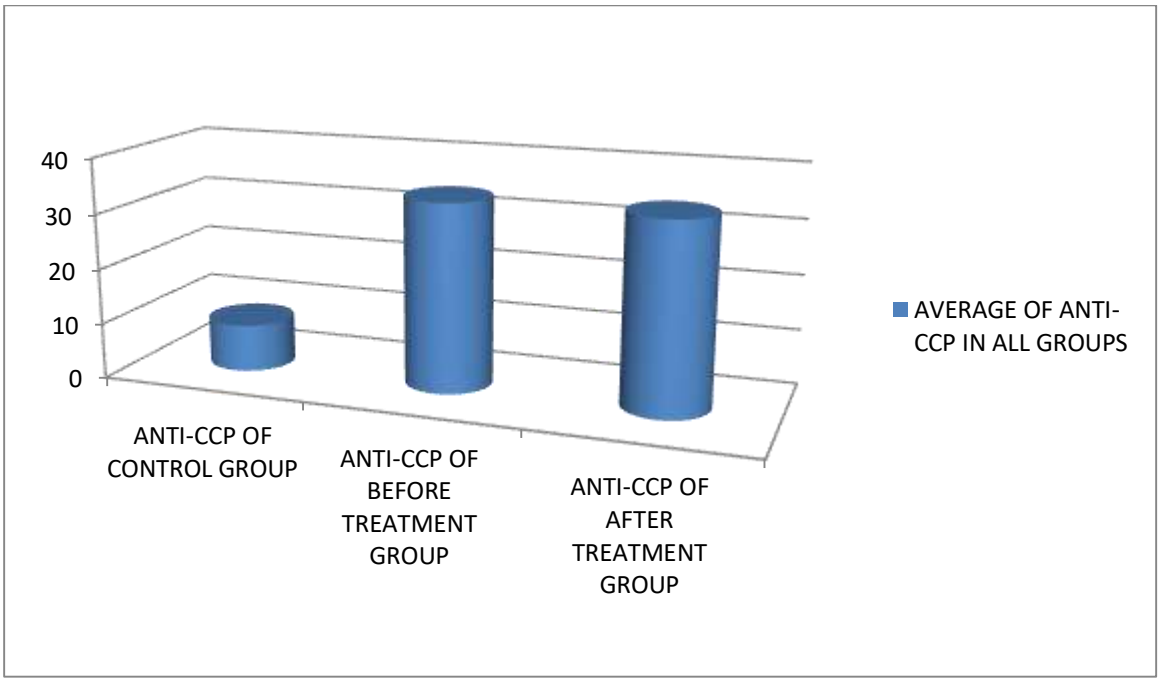

Figure 3 Average levels of control, before and after treatment groups of ANTI-CCP

ANTI-CCP levels are low in control group and are high in patients no significant change was applied to it after treatment.

TABLE 3Correlation analysis of patients before treatment

	IL 17A	IL 17AR	ANTI- CCP
IL 17A	1	0.89	-0.23
IL 17AR	0.89	1	-0.25
ANTI- CCP	-0.23	-0.25	1

The correlation of patients before treatment is normal except for IL17A which have a very strong correlation with IL17AR (0.89) it shows that the IL17A and IL17AR have high relation with disease severity.

TABLE 4 Correlation analysis of patients after treatment

	IL 17A	IL 17AR	ANTI- CCP
IL 17A	1	0.78	0.76
IL 17AR	0.78	1	0.81
ANTI- CCP	0.81	0.76	1

High correlation of patients after treatment between IL17A and IL17AR, ANTI-CCP (0.78 and 0.81). Another strong correlation observed that IL17AR with IL17A, ANTI-CCP (0.78 and 0.76). And finally ANTI-CCP correlation come as follow IL17A – 0.76, IL17AR 0.8

III. Discussion:-

This study which was done on psoriasis patients in Iraq included 90 individual, 60 patients were diagnosed with psoriasis (30 patient before treatment and 30 patients after treatment) and 30 healthy individual. According to age parameter table 1 show that the ranged age of psoriases patients before treatment starts from age 10 years to 70 years and the patient of psoriasis were mostly high in the age of 25-39 and 40-54 years old.

For each patient whose form was completed under the supervision of a consultant, the patients were divided into two groups with regard to gender (males:34 and females:26) and also with regard to treatment in to two groups before treatment (30 patients) and after treatment (30 patients) and patient were identified with psoriatic arthritis and patients without psoriatic arthritis. Where patients with psoriatic arthritis have a ANTI-CCP ratio (<0.20) and patients with ratio of (>0.20) means that the patient does not have psoriatic arthritis.The mean age of control group (39.23±13.75/32.94±11.60) male and female respectively [11].

As shown in Table 1, psoriasis mostly affects at the age of 25 to 55 and is average until the end of middle age, no significant change in P values of IL-17A and IL-17AR. There a significant change between IL17A and all age's groups with P value (< 0.0001), another significant change is with IL17AR with P value (< 0.0001). During plaque psoriasis pathogenesis IL-17A plays a central role. It is elevated in psoriatic skin lesions and promotes multiple pro-inflammatory molecules, particularly by keratinocytes, from the local output. Psoriasis is effective in neutralizing the antibodies against IL-17A and its receptor [15].

Table 2 results which is after treatment, p value levels aresimilar to these results of both before and after treatments, there is a significant change with all parameters IL17A, IL17AR AND ANTI-CCP P value at a different aging range are all (<0.0001) and these results goes with [11]. Psoriasis can happen at any age. Although some research suggested the average onset age for psoriasis was 33 years of age, and 75 percent of cases occurred before age 46, which goes against [16]. Others indicated that the progression of psoriasis was bimodal with two disease peaks-the first between 16 and 22 years of age and the second between 57 and 60.

These pro-inflammatory cytokines can stimulate keratinocytes and endothelial cells in the skin by binding to the IL-17 receptor, resulting in skin inflammation and progression of the disease[17]. Hence, a variety of biological agents targeting the IL-23/Th17 pathway have shown robust efficacy in the clinic and have recently been approved for the treatment of mild to serious plaque psoriasis [18].

Average levels of infected patients of before and after treatment and control group.

Different serum levels of all groups' shows the changes of each process done through the Figures.

We can clearly observe the serum levels change of before and after treatment as the levels of IL17A, IL17AR down after treatment while they are normal in control group. These results go with [19]. The correlation between high serum IL-17A and high severity of the disease supports the hypothesis that psoriasis is a severe low serum IL-17A disease following effective treatment with psoriasis, although the skin is primarily affected. Another study that goes opposite with our study [20]. It was demonstrated that IL-17A cytokines were higher in serum in psoriasis patient's more than healthy controls. However, we found no association between systemic and cytokine expression the severity of the disease. Other researchers suggested that, it was established that the anti-CCP titer was associated with disease activity in RA [22].

The patient's analysis of before and after treatment correlation groups

Table 3 show The correlation of patients before treatment doesn't have high correlation it just show a correlation between IL17A and a very strong correlation with IL17AR (0.89) it shows that the IL17A and IL17AR have high relation with disease severity this goes with [22]. The higher intensity IL-17A Serum Disease Association further supports the idea that while the skin is mainly affected, psoriasis is a systematic disease [23]. High blood levels of IL-17A in psoriasis patients before treatment with etanercept and acitretin [24]. indicated a positive relationship between IL-17 and disease activity in skin

lesions of patients with psoriasis [25]. indicated a positive correlation between the serum IL-17 levels and PASI. And goes opposite with [26]. Who could not demonstrate any association between IL-17A serum levels and disease activity.

In the current study, in a broad cohort of patients with psoriasis, we observed that baseline serum IL17A responded moderately to disease severity. Other independent studies [22] have reported similar correlations. The correlation of high serum IL-17A with greater severity of the disease supports the idea that psoriasis, while predominantly affected by the skin, is a systemic disorder.

The patient's correlation analysis of after treatment groups

Table 4 showsthe correlation of patients after treatment show high correlation between IL17A and IL17AR, ANTI-CCP (0.78 and 0.81). Another strong correlation observed that IL17AR with IL17A, ANTI-CCP (0.78 and 0.76). And finally ANTI-CCP correlation come as follow IL17A – 0.76, IL17AR 0.81. These correlation results came after the treatment and it shows that all of the tests have strong effect on psoriasis. These results go with [25]. Increased serum levels IL-12, IL-17 associated with PASI In addition, cytokine levels dropped following diagnosis with psoriasis[27]. It indicated that high IL-17 levels aren't associated with PASI. Nonetheless, it is interesting that all papers reported substantial association between IL-17 and PASI although no difference was observed between psoriatic patients and controls in the serum levels of IL-17 [28].

Some inflammatory cytokines are affected in serum psoriasis patients. Moreover, it found a significant correlation between disease severity and serum levels IL-12 and IL-17 [29]. Noticed that anti-CCP antagonists were more frequent in the RA subgroup of high levels of cytokines [30].A strong correlation has been established between the presences of CCP antibodies in the PsA.

The relationship between IL-17 and TNF-α is further complicated as they function synergistically to co-regulate several keratinocyte genes strongly expressed in psoriatic skin lesions. Together, these findings suggest that IL-17A and TNF-α function through distinct mechanisms to regulate downstream gene expression, with the IL-23/IL-17A axis at the center of pathogenesis of psoriasis, and TNF-α playing a more ancillary role in promoting inflammation via synergism with IL-17A and the formation and maturation of myeloid dendritic cells[31]. This hypothesis is further supported by evidence that inhibition of IL-17A alone is highly successful for psoriasis and PsA in the absence of inhibition of TNF-α [32].

Targeting IL-17 receptor A with brodalumab is also highly effective, and it inhibits IL-17A mediated signaling. Brodalumab also normalizes psoriatic lesional skin transcript to me, the gene expression profile associated with IL-17A, IL-17C and IL-17F, decreases rates along with inflammatory mediators derived from keratinocytes [33].

It was found that 20% and 42% of patients of autoimmune skin disease had raised anti-CCP respectively. When these patients were categorized in two groupswith arthritis and without arthritis, we

found a higher level of anti-CCP in Group containing arthritis. But this increase was significant only for anti-CCP. This finding was consistent with the finding of [34].

IV. Conclusion:-

IL17A, IL17AR and ANTI-CCP were elevated in all patients of psoriasis and were lowered in all patients after treatment. They are a very good follows - up marker for diagnoses and treatment of psoriasis and Psoriasis Arthritis, so both of them are very good markers for follow up.

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