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Original Article

Assessment of tumor necrosis factor alpha and interleukin-10 in obese psoriatic patients before and after using apremilast

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Abstract

Background Psoriasis is one of the most prevalent chronic inflammatory skin conditions; its prevalence ranges from 1 to 3%. Tumor necrosis factor-alpha (TNF-α), a cytokine that enhances inflammation, is overexpressed in synovium and skin plaques in psoriasis. TNF-α plays a critical role in the pathogenesis of psoriasis. IL-10 is the most crucial cytokine for reducing excessive immune responses and decreasing pro-inflammatory reactions in all autoimmune disorders.

Objective To evaluate the effect of Apremilast on IL-10, TNF-α, and BMI in obese psoriatic patients.

Methods Thirty patients included in this investigative study to measure the concentrations of TNF-α, IL-10 and BMI, before and after receiving Apremilast. TNF-α and IL-10 were examined by ELISA technique.

Results The present work found that the concentration of TNF-α before receiving Apremilast was 286.80 pg/ml, and after six months from baseline, it was reduced to 131.08 pg/ml ($P<0.01$). Also, IL-10 before using Apremilast was 69.28 pg/ml, and after six months of treatment it increased to 112.57 ±7.89, which was statistically significant ($P<0.01$). There were no statistically significant differences in BMI ($P>0.05$).

Conclusion Apremilast significantly reduced the inflammatory cytokine TNF-α and increased the anti-inflammatory cytokine IL-10, leading to improvement in psoriasis lesions. It also reduced Body Mass Index in obese psoriatic patients.

Key words
Apremilast; IL-10; Obesity; TNF-α; Psoriasis.

Introduction

Psoriasis is a chronic inflammatory skin condition characterized by erythematous plaques with distinct borders and white scales.[1] Psoriasis is one of the most prevalent chronic inflammatory skin conditions; its prevalence ranges from 1 to 3%.[2] It affects males and females equally. The bimodal distribution of psoriasis shows a peak between the ages of 15 and 20 and another between the ages of 55 and 60.[3] In 2014, the FDA approved oral use of Apremilast. Apremilast is an oral PDE4 inhibitor that regulates inflammatory mediators, including those involved in the etiology of psoriasis, intracellularly.[4] PDE-4 inhibitors enhance cAMP levels and decrease the expression of pro-inflammatory mediators like TNF-α, IL-2, IL-12, and IL-23 by preventing cAMP from being

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destroyed. PDE-4 inhibitors stimulate the CREB factor, which in turn increases the synthesis of anti-inflammatory cytokines like IL-10.[5,6]

Elevated levels of TNF-α are found in both blood and lesional skin of individuals with active psoriasis.[7] Anti-TNF-α therapies have been successful in treating psoriasis and psoriatic arthritis, which inhibit TNF-α, reducing inflammation and improving clinical outcomes.[8] Interleukin 10 (IL-10) is a cytokine with strong anti-inflammatory properties. Dysregulation of IL-10 is associated with enhanced immuno-pathology in response to infection and increased risk for development of many autoimmune diseases.[9]

Obesity and psoriasis are correlated in two ways: Obesity can predispose people to psoriasis, and psoriasis can contribute to obesity through social isolation, poor eating habits, and reduced physical activity. Additionally, obesity impacts how well psoriasis patients respond to treatment because it alters the pharmacokinetics of medications, boosts drug clearance, and lowers serum levels.[11] There aren't many studies on how Apremilast affects IL-10, TNF-α, and its effects as a treatment for psoriasis sufferers. For that reason, the purpose of this study was to find out how the Apremilast medication affected the concentrations of IL-10, TNF-α, and BMI in obese psoriatic patients.

Methods

This investigative study was conducted at Dermatology Center, Medical City in Baghdad/Iraq. Between November 2021 to December 2022. After full explanation for each patient about the nature of disease, course prognosis, treatment and complications by Dermatologist, in addition to the target of this study, Formal consent was taken from each patient before starting the study. Ethical Approval by Development Department of Medical City Directorate in Baghdad-Iraq**.**

A total of 30 patients attending the outpatient clinic were enrolled in the study. These patients were receiving Apremilast (Aprezo)® manufactured by Glenmark Pharmaceuticals Ltd. administered twice daily after food (approximately 12 hours apart) for six months. Six of them did not complete the study due to different reasons.

Blood samples were taken from all patients before receiving Apremilast at baseline for measurement of TNF-α and IL-10 levels respectively. The BMI of each patient was assessed according to the international standard measurement "[BMI=weight(kg)/height(m)^2]". Baseline BMI were measured and monitored monthly.

The practical side performed at Baghdad Hospital-Medical City directorate and the International Center for Research and Development (ICRD). Human TNF-a and IL-10 ELISA kit provide by ELK Biotechnology-China.

“The Statistical Analysis System- SAS (2018) program was used to detect the effect of difference between the two groups in study parameters, T-test was used to significant compare between means, Chi-square test was used to significant compare between percentage” (0.05 and 0.01 probability).[12]

Result

Interleukin 10 (IL-10) and tumor necrosis factor alpha (TNF-α) The current work found the concentration of TNF-α before receiving Apremilast was (286.80 pg/mL), and after six months from baseline it decreased to (131.08 pg/mL), which was statistically significant

(P<0.01). While the concentration of IL-10 before treatment with Apremilast was (69.28 pg/mL), after six months of treatment it increased to (112.57 pg/mL), which was statistically significant (P<0.01) as shown in **Table 1**.

Body Mass Index The international standard measurement of body mass index was used as an indicator to measure the body mass index of all cases. There was no significant difference (P>0.05) in BMI before and after receiving Apremilast, but after six months of treatment with Apremilast the BMI was reduced by 2.5 Kg/m^2 as shown in **Table 2**.

Age group The average age of the group was 38 years. The most common age group was 30-40 years, about 60%, followed by >40 years which was about 26.6%, as illustrated in **Table 3**.

Discussion

Psoriasis is an immunological disease in which many cytokines are involved, such as TNF-α and IL-10. In our study, Apremilast affected the inflammatory cytokine, which led to a reduction in TNF-α and an enhancement of the anti-inflammatory cytokine IL-10. To the best of our knowledge, this is the first study to assess the concentrations of TNF-α and IL-10 in obese psoriatic patients before and after receiving Apremilast treatment in Iraq.

Table 1 Comparison of TNF-α and IL-10 levels before and after receiving apremilast.

Group	*Mean±SD*	
	IL-10 (pg/mL)	*TNF-α (pg/ml)*
Patients: Before treatment	69.28 ±2.12	286.80 ±16.40
Patients: After treatment	112.57 ±7.89	131.08 ±2.43
T-test	14.675 **	37.932 **
P-value	0.0001	0.0001

** (P<0.01).

IL-10: Interleukin-10. TNF-α: Tumor Necrosis Factor alpha.

Table 2 Comparison of BMI before and after receiving apremilast.

Group	*Mean±SD BMI (kg/m2)*
Patients: Before treatment	32.97 ±1.07
Patients: After treatment	30.48 ±1.14
T-test	3.175 NS
P-value	0.349

BMI: Body Mass Index, NS: Non-Significant.

Table 3 Distribution of study sample according to age of patients.

Age group (year)	*No*	*Percentage (%)*
<30 yr.	4	13.33
30-40 yr.	18	60.00
>40 yr.	8	26.67
Total	30	100%
P-value	-	0.0052 **

** (P<0.01).

Moreover, according to *Mavropoulos et al*;[13] Apremilast enhanced IL-10-producing B-reg cells, which control inflammation, in individuals with psoriatic arthritis and psoriasis. Additionally, after twenty-four weeks, Apremilast decreased blood levels of TNF-α.[14] Also, after forty weeks, Apremilast decreased serum levels of Interleukin 6 and increased Interleukin 10.[14] This study is consistent with other recent research, which found that Apremilast's mode of action intervenes earlier in the inflammatory cascade than the biologic medicines that inhibit TNF-α, IL12/23, IL-17, and their receptors.[15] Apremilast inhibits the PDE4 enzyme and modulates the immune system by increasing levels of intracellular cyclic adenosine monophosphate (cAMP) and inhibiting tumor necrosis factor (TNF-α) production. Moreover, Apremilast significantly reduced symptoms of diseases with particular sites of involvement, such as palmoplantar, nail, and scalp psoriasis. It also enhanced patient quality of life and reduced pruritus symptoms.[16,17]

Accordingly, the BMI was reduced by 2.5 Kg/m^2 at 6 months after receiving Apremilast, which was not statistically significant. The

present study is consistent with *Ferguson et al.*[18] which showed that Apremilast, used to treat psoriasis, had some impact on BMI. Weight loss and BMI reduction after 6 months of treatment with Apremilast have been found to be associated with mild weight loss and a BMI reduction. The *Ferguson et al.* study showed a 2.2 kg weight loss and a 0.8 kg/m^2 BMI reduction.

The average age of the patients in this study was 38 years old. A study by *Iskandar I et al.*[19] demonstrated that psoriasis development follows a bimodal age pattern, with the first peak occurring between 30-39 years old and the second peak between 60-69 years old. However, over a 30-year period, two studies conducted in the USA showed that new cases of psoriasis are increasing in both children and adults.[20]

Conclusion

Apremilast as a monotherapy is effective in reducing the inflammatory cytokine TNF-α, which leads to improvement in psoriasis lesions. Moreover, it significantly increases the anti-inflammatory cytokine IL-10, which plays a strong role in several immune reactions, including regulatory mechanisms in the skin and anti-psoriatic action. This study found that Apremilast was associated with a reduction in BMI after 6 months from baseline, with a reported reduction in BMI of 2.5 Kg/m^2.

References

1. Boehncke W, Schön M. Disease burden and epidemiology. *Lancet*. 2015;**386**:983-94.
2. Abdulridha SH, Kadhim DJ, Razzak SAA. Beliefs about Medicines among a Sample of Iraqi patients with Psoriasis. *Innov Pharm*. 2021;**12(1)**:10.24926/iip.v12i1.3584..
3. Flytström I. Different aspects of psoriasis etiology and treatment. 2012 May 14.
4. Afra T, Razmi TM, Dogra S. Apremilast in psoriasis and beyond: big hopes on a small molecule. *Indian Dermatol Online J*. 2019;**10(1)**:1.
5. Milakovic M, Gooderham MJ. Phosphodiesterase-4 inhibition in psoriasis. *Psoriasis: Targets and Therapy*. 2021:21-9.
6. Gao JC, Wu AG, Contento MN, Maher JM, Cline A. Apremilast in the Treatment of Plaque Psoriasis: Differential Use in Psoriasis. *Clin Cosm Investig Dermatol*. 2022:395-402.
7. Yost J, Gudjonsson JE. The role of TNF inhibitors in psoriasis therapy: new implications for associated comorbidities. F1000 medicine reports. 2009;1.
8. Kane D, FitzGerald O. Tumor necrosis factor-α in psoriasis and psoriatic arthritis: A clinical, genetic, and histopathologic perspective. *Curr Rheumatol Rep*. 2004;**6(4)**:292-8.
9. Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. *Crit Rev Immunol*. 2012;**32(1)**:23-63.
10. Abdulridha SH, Kadhim DJ, Razzak SAA. Assessment of Quality of Life in a Sample of Iraqi Patients with Psoriasis. *Iraqi J Pharm Sci*. 2020;**29(2)**:161-8.
11. Puig L. Obesity and psoriasis: body weight and body mass index influence the response to biological treatment. *J Eur Acad Dermatol Venereol*. 2011;**25(9)**:1007-11.
12. SAS S. Statistical Analysis System, User's Guide. Statistical. Version 9.6. SAS Inst Inc Cary NC USA. 2018.
13. Mavropoulos A, Zafiriou E, Simopoulou T, Brotis AG, Liaskos C, Roussaki-Schulze A, *et al*. Apremilast increases IL-10-producing regulatory B cells and decreases proinflammatory T cells and innate cells in psoriatic arthritis and psoriasis. *Rheumatol*. 2019;**58(12)**:2240-50.
14. Schafer PH, Chen P, Fang L, Wang A, Chopra R. The pharmacodynamic impact of apremilast, an oral phosphodiesterase 4 inhibitor, on circulating levels of inflammatory biomarkers in patients with psoriatic arthritis: substudy results from a phase III, randomized, placebo-controlled trial (PALACE 1). *J Immunol Res*. 2015.
15. Gialouri CG, Evangelatos G, Fragoulis GE. Choosing the Appropriate Target for the Treatment of Psoriatic Arthritis: TNFα, IL-17, IL-23 or JAK Inhibitors?. *Mediterranean J Rheumatol*. 2022;**33(Suppl 1)**:150.

16. Armstrong AW, Puig L, Joshi A, Skup M, Williams D, Li J, *et al*. Comparison of biologics and oral treatments for plaque psoriasis: a meta-analysis. *JAMA Dermatol*. 2020;**156(3)**:258-69.
17. Sbidian E, Chaimani A, Garcia-Doval I, Doney L, Dressler C, Hua C, *et al*. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev*. 2022;**5(5)**:CD011535..
18. Ferguson LD, Cathcart S, Rimmer D, Semple G, Brooksbank K, Paterson C, *et al*. Effect of the phosphodiesterase 4 inhibitor apremilast on cardiometabolic outcomes in psoriatic disease—results of the Immune Metabolic Associations in Psoriatic Arthritis study. *Rheumatol*. 2022;**61(3)**:1026-34.
19. Iskandar I, Parisi R, Griffiths C, Ashcroft D, Atlas GP. Systematic review examining changes over time and variation in the incidence and prevalence of psoriasis by age and gender. *Br J Dermatol*. 2021;**184(2)**:243-58.
20. Tollefson MM, Crowson CS, McEvoy MT, Kremers HM. Incidence of psoriasis in children: a population-based study. *J Am Acad Dermatol*. 2010;**62(6)**:979-87.