Analysis of Inflammatory Factors Levels and Safety in the Treatment of Psoriasis with Apremilast

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To analyze the levels of inflammatory factor and safety in treating psoriasis with apremilast, we selected 200 cases of psoriasis patients under-treated in our hospital from January 2021 to January 2022, divided them into control group and experimental group at random, 100 cases, respectively. Control group received normal treatment, while treated experimental group with apremilast. Compare both groups on the levels of inflammatory factors, psoriasis skin lesions and adverse drug reactions. Before treatment, both groups had no statistical difference on serum inflammatory factor levels, but they improved after treatment. Experimental group had more obvious improvement after treatment; it had higher interleukin-10 level than control group, but it possessed lower tumour necrosis factor alpha, interferon gamma, interleukin-23, interleukin-7 and interleukin-6 levels than control group ($p<0.05$). The psoriasis area and severity index score of both groups decreased after 4 w treatment and at the end of treatment compared before treatment, but experimental group possessed lower psoriasis area and severity index score after treatment than control group ($p<0.05$). The adverse drug reactions rate was 7.00 % in control group and 11.00 % in experimental group, the difference possessed no statistical significance ($p>0.05$). There was a certain efficacy and safety in treating psoriasis by apremilast, which can inhibit inflammatory factors level and improve the condition of skin lesions effectively. It is worth popularizing.

Key words: Psoriasis, apremilast, inflammatory factors, dermatitis

Psoriasis is a chronic relapsing inflammatory disease caused by immune dysfunction in human body. In recent years, some studies have proposed Phosphodiesterases (PDEs) as new therapeutic targets, which can degrade intracellular second messengers (such as cyclic Adenosine Monophosphate (cAMP), cyclic Guanosine Monophosphate (cGMP) etc.,) and has an important effect on regulating cell activities. Among them, Phosphodiesterase-4 (PDE-4), as the main PDE subtype in immune cells, has been proven to regulate the metabolism of various pro-inflammatory and anti-inflammatory mediators. Therefore, clinical attempts have been made to apply it in the treatment of skin diseases such as atopic dermatitis, psoriasis and vitiligo, and achieved good results[1]. Apremilast is an oral PDE-4 inhibitor currently clinically used for treating psoriasis, which has the effect of inhibiting inflammatory response in human body[2]. However, there is still not enough medical evidence in domestic and foreign studies to prove that apremilast has an effect on the changes of inflammatory factor activity in psoriasis and its drug safety[3,4]. Therefore, this study specially selected 200 psoriasis patients as the research objects and carried out random group comparison to study the effect of apremilast. Selected 200 cases of psoriasis patients under-treated in our hospital from January 2021 to January 2022, divided them into control group and experimental group at random, 100 cases, respectively. The proportion of male and female patients in control group was 58:42, the minimum age was 35 y old, the maximum age was 78 y old, so the median value was (46.79±8.32) y old; the shortest course of disease was 1 y, the longest course of disease was 8 y, so the median value was (3.57±2.84) y. 35 cases mild psoriasis, 37 cases moderate psoriasis and 28 cases severe psoriasis included. The proportion of male and female patients in experimental group was 55:45, the minimum age was 32 y old, the maximum

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age was 80 y old, so the median value was (45.21±9.02) y old; the shortest course of disease was 1 y, the longest course of disease was 8 y and the median value was (3.19±3.05) y. 40 cases mild psoriasis, 35 cases moderate psoriasis and 25 cases severe psoriasis included. Both groups possessed no remarkable difference on general data ($p>0.05$), so the study can be carried out. Inclusion criteria meets the diagnostic standard of the "Guideline for the diagnosis and treatment of psoriasis in China (2018 complete edition)" and had relevant symptoms[5]; all patients and their families were informed about the study and signed the informed consent. Exclusion criteria has, combined with other skin diseases; combined with severe liver organ and cardiovascular and brain diseases; combined with immune system diseases; combined with coagulation dysfunction; combined with mental illness or cognitive impairment and history of drug treatment such as glucocorticoid or tretinoin within 3 mo before enrollment. Treated control group with placebo ointment, that is, external coating compound flumetasone ointment (Bright Future Pharmaceutical Factory, GYZZ HC20140031, specification 15 g) to the affected area, 1-2 times/d. Advised patients to pay attention to their diet, which should be light and avoid spicy and greasy. After receiving the same treatment as control group, treated experimental group with apremilast, 20 mg/time, 2 times/d. Both groups were treated for 16 w. At admission and after 16 w treatment, collected 2 ml of venous blood from the patient's elbow in the morning and detected by Enzyme-Linked Immunosorbent Assay (ELISA), including serum Interleukin-10 (IL-10), Tumor Necrosis Factor Alpha (TNF-α), Interferon Gamma (IFN-γ), Interleukin-6 (IL-6), Interleukin-17 (IL-17) and Interleukin-23 (IL-23). Adopted Psoriasis Area and Severity Index (PASI) as an assessment tool to assess patients 'condition at admission, after 4 w of treatment and at the end of treatment. The scoring criteria are as follows: The scoring parts of skin lesion area include head and neck, upper limbs, trunk and lower limbs. Among them, there is no rash (0 points), the rash area is less than 10 % (1 point), the rash area range is 10 %-29 % (2 points), the rash area range is 30 %-49 % (3 points), the rash area range is 50 %-69 % (4 points), the rash area range is 70 %-89 % (5 points) and the rash area range is ≥90 points (6 points); the severity of skin lesions is divided into three types: Erythema, infiltration and scaling. Among them, not severe (0 points), mild (1 point), moderate (2 points), severe (3 points) and extremely severe situation (4 points). The total score of the scale ranges from 0 to 72. The higher the score, the more serious the condition is[6]. Adverse drug reactions include itching, rash, headache, nausea, diarrhea and upper respiratory tract infection. Adopted Statistical Package for the Social Sciences (SPSS) 20.0 to process and analyze data. Used ($\bar{x}\pm s$) to express the measurement data and tested by t, expressed the enumeration data by n % and tested by Chi-square (χ^2). The results showed that $p<0.05$, indicated that the comparison possessed statistical significance. Before treatment both groups had no significant difference on serum inflammatory factor levels, but they improved after treatment compared before treatment; experimental group improved more obviously after treatment: IL-10 level was higher than control group, but TNF-α, IFN-γ, IL-23, IL-17 and IL-6 levels were lower than control group ($p<0.05$) as shown in Table 1. The PASI scores of both groups after 4 w treatment and at the end of treatment were lower compared before treatment, but after treatment experimental group possessed lower PASI scores than control group ($p<0.05$), as shown in Table 2. The adverse drug reactions rate of control group was 7.00 % and that in experimental group was 11.00 %. The differences of both groups had no statistical difference ($p>0.05$), as shown in Table 3. At present, the pathogenesis of psoriasis has not been clearly defined in clinical practice, but according to relevant reports, psoriasis is an inflammatory disease mediated by cellular immunity under the combined action of internal and external factors and environmental factors. Under the interaction of immune cells and inflammatory factors, the immune regulation of the body is unbalanced, which leads to psoriasis[7]. Common symptoms of psoriasis include skin rash, bright red basal skin color, scaly erythema, shiny film phenomenon after scraping off the scales, thick scales and spotting bleeding[8]. The drugs currently used for treating psoriasis include glucocorticoids, TNF blockers and IL-12/IL-23 inhibitors, but the clinical application of these drugs all have certain limitations[9]. Therefore, PDE-4 inhibitors, as a new type of psoriasis treatment drug, have received good feedback as soon as they are proposed. Apremilast had got approval from the United States Food and Drug Administration in 2014 for treating psoriasis, which can effectively inhibit the activity of PDE-4. Its pharmacological effect is to increase the level of cAMP, inhibit various pro-inflammatory factors such as IL-23, TNF-α and IFN-γ, down-regulate pro-inflammatory cytokines expression

and finally inhibit the body's inflammatory response to improve the symptoms of psoriasis[10]. Results of this study firstly compared to inflammatory factor levels in psoriasis patients under conventional placebo treatment and apremilast treatment and found that after treatment, serum inflammatory factors levels of both groups improved compared before treatment; the improvement of experimental group after treatment was more significant: IL-10 level was higher than control group, but TNF-α, IFN-γ, IL-23, IL-7 and IL-6 levels were lower than control group ($p<0.05$). It is suggested that apremilast treatment can inhibit immune and inflammatory responses and have important effect on the pathogenesis and prognosis of psoriasis. Luo *et al.*[11] mentioned in a study on the expression level of PDE-4 subtype mRNA in atopic dermatitis and psoriasis skin lesions and its role in the pathogenesis that PDE was the master regulator of cAMP and PDE-4 was the main PDE subtype in immune cells. As an oral PDE-4 inhibitor, apremilast could be taken orally into the body to inhibit intracellular PDE4, which could accumulate cAMP in the body. Thus, pro-inflammatory cytokines expression levels such as TNF-α, IL-23 and other inflammatory mediators IL-7, IFN-γ reduced, anti-inflammatory mediators levels such as IL-10 increased, and pro-inflammatory and anti-inflammatory mediators in cells was regulated to achieve anti-inflammatory effect. Zhang *et al.*[12] research results on the treatment of alopecia areata with topical PDE-4 inhibitor ointment are consistent with this study, which further confirms that apremilast, as a representative new drug of PDE-4 inhibitor, can effectively regulate the activity of serum inflammatory factors in patients with psoriasis, promote the pathological process of anti-inflammatory and anti-inflammatory and has ideal curative effect. In addition, clinical trials have found that it has a pharmacological effect on reducing the degree of tissue lesions of psoriasis plaque and reducing the thickness of epidermis. Another result of this study compared the PASI scores before and after treatment and found that after 4 w treatment, at the end of treatment and after treatment, the PASI scores of both groups were lower than treatment before, but experimental group possessed remarkably lower PASI scores than control group. It can be considered that the anti-inflammatory pharmacological effect of apremilast can effectively improve the skin lesions of patients. Analysis of the reasons was IFN-γ in the body has paracrine and autocrine effects, which in turn leads to the proliferation of human skin keratinocytes and inflammation, while TNF-α is widely distributed in the inflammatory cells infiltrated around the epidermis and dermal blood vessels in the skin lesions of psoriasis patients and the severity of skin lesions in patients is positively correlated with the levels of IFN-γ and TNF-α[13,14]; in addition, IL-6 is related to psoriasis cell dynamics. IL-6 has the effect of promoting the proliferation of cultured keratinocytes[15], indicating that it can lead to psoriasis lesions and skin proliferation. Therefore, the decrease of IL-6 can also reduce the thickness of the epidermis. It is reported that the absolute bioavailability of apremilast is about 73 % and its concentration in plasma reaches a median of about 2.5 h after oral intake. Even if other foods are ingested at the same time, it does not affect the clinical activities of patients. At the same time, it can be extensively metabolized through the oxidation mechanism and hydrolysis mechanism in the body, with fast onset and good curative effect[16]. The inflammatory response of patients with psoriasis was inhibited after apremilast treatment, thereby reducing the PASI score of the patients, suggesting the good efficacy of apremilast in treating psoriasis. Finally, comparing the adverse reactions of both groups, the results showed that the differences of both groups possessed no statistical significance, but it could be seen that most of the adverse reactions of apremilast were mild reactions, such as itching, rash, headache, nausea, diarrhea and upper respiratory tract infection. etc., and according to the feedback of patients, the adverse reactions could be relieved spontaneously after a period of time and as a small molecule drug, oral administration was more convenient than the injection administration of biological agents and the degree of acceptance of patients was higher. It is worth noting that apremilast is a drug with high safety and tolerance, but because it is a recently marketed drug, its clinical application cases are still limited and there are few control trial research samples collected, which has certain one-sidedness and limitations. Although the sample number of 200 cases selected in this study is large and the results have certain corroboration, more in-depth clinical research is still needed to confirm its efficacy and safety. In conclusion, apremilast has a certain curative effect and safety in the treatment of psoriasis, can effectively inhibit inflammatory factors level, and improve the skin lesions, which is worthy of promotion.

TABLE 1: COMPARISON OF SERUM INFLAMMATORY FACTOR LEVEL CHANGE OF BOTH GROUPS BEFORE AND AFTER TREATMENT (x̄±s)

Group	IL-10 (ng/l)		TNF-α (ng/l)		IFN-γ (ng/l)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=100)	32.75±5.95	40.57±4.41*	75.31±8.25	40.35±6.43*	28.74±2.52	32.15±6.23*
Experimental group (n=100)	32.57±5.02	50.29±4.31*	75.24±7.02	30.18±5.36*	28.29±2.31	38.39±4.95
t	0.231	15.763	0.065	12.149	1.319	7.842
p	0.817	0	0.949	0	0.189	0
Group	**IL-6 (pg/ml)**		**IL-17 (pg/ml)**		**IL-23 (pg/ml)**	
Control group (n=100)	60.38±5.72	45.89±8.54*	34.95±6.23*	29.71±8.12	60.57±5.41	28.39±4.19
Experimental group (n=100)	60.31±4.98	29.77±8.06*	35.05±5.97	20.64±8.15	60.29±4.35	20.06±4.55
t	0.092	13.727	0.116	7.884	0.403	13.467
p	0.927	0	0.908	0	0.687	0

Note: Compared with the same group before treatment, *p<0.05

TABLE 2: COMPARISON OF PASI SCORES OF BOTH GROUPS BEFORE AND AFTER TREATMENT (points, x̄±s)

Group	On admission	After 4 w treatment	After treatment
Control group (n=100)	39.21±8.55	35.32±9.73	33.95±8.19
Experimental group (n=100)	40.02±8.03	30.17±10.26	21.32±6.46
t	0.691	3.642	12.108
p	0.491	0	0

TABLE 3: COMPARISON OF ADVERSE DRUG REACTIONS OF BOTH GROUPS (n %)

Group	Itching	Rash	Headache and nausea	Diarrhea	Upper respiratory tract infection	Incidence of adverse drug reactions
Control group (n=100)	2 (2.00)	5 (5.00)	0 (0.00)	0 (0.00)	0 (0.00)	7 (7.00)
Experimental group (n=100)	1 (1.00)	5 (5.00)	2 (2.00)	1 (1.00)	2 (2.00)	11 (11.00)
χ^2			0.977			
p			0.323			

Conflict of interests:

The authors declared no conflicts of interest.

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