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Original Research Article

Evaluation of ustekinumab treatment in psoriasis and the potential effect of metabolic syndrome on treatment response: a single center retrospective study

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ABSTRACT

Background: Ustekinumab is a biological agent used in the treatment of psoriasis. This study evaluated the treatment response of psoriasis patients who received ustekinumab.
Methods: The study included nine patients with plaque-type psoriasis who received ustekinumab treatment. Clinical response of all patients was evaluated with psoriasis area and severity index (PASI), dermatology life quality index (DLQI), and psoriasis disability index (PDI) at 0, 4, 16 and 28 weeks. The patients were also evaluated for metabolic syndrome and its effect on treatment response.
Results: A total of five male and four female patients with psoriasis vulgaris were included in the study. At the end of 28th weeks, 55% of the patients reached PASI 75 score. The mean PASI scores of the patients at weeks 0, 4, 16, 26 and 28 were 36.98±12.28, 8.86±9.06, 9.52±11.55, 3.55±3.61 and 6.98±6.40, respectively. Although not statistically significant, at the 28th weeks, the mean PASI, DLQI and PDI values of the patients with metabolic syndrome were higher than those without metabolic syndrome (p=0.505, p=0.314, p=0.786, respectively).
Conclusions: Ustekinumab is an effective treatment option for patients with psoriasis who resistant to conventional and biological treatments. In resistant cases to the ustekinumab, the routine treatment interval should be reduced. Psoriasis patients with accompanying metabolic syndrome may have a lower response rate than those without metabolic syndrome to biological agents.

Keywords: PASI score, Quality of life, Ustekinumab, Metabolic syndrome

INTRODUCTION

Biological agents have been used for certain diseases in dermatological diseases since they were approved for the treatment of moderate to severe psoriasis in 2003.[1] They are protein molecules produced by recombinant DNA technology that target specific points in the immunopathogenesis of the diseases.[2,3] Ustekinumab (UST) is a biological agent that inhibits signaling pathways activated by IL-12/23. It is a human IgG1k monoclonal antibody that binds with specificity to the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 cytokines.[4,5] Since its approval for psoriasis in 2009 by the FDA, it has been compared with other biological agents in numerous studies.[6,7] In this study, the clinical and demographic characteristics of patients who received UST due to resistance to previous treatments were evaluated. Psoriasis area and severity index (PASI),

psoriasis disability index (PDI) and the Dermatology Life Quality Index (DLQI) were used to assess the efficacy of UST. Furthermore, to our knowledge, there is no sufficient studies on the relationship between metabolic syndrome and UST treatment. Therefore, we also investigated the relationship between metabolic syndrome and UST treatment in patients with psoriasis.

METHODS

Study design

This is a single-center, retrospective study. The study included 9 plaque-type psoriasis patients who were resistant to conventional/anti-TNF agent's treatment and received UST treatment for at least six months. The dose of UST for an adult patient with psoriasis weighing up to 100kg was 45mg (one injection) at week 0, one injection at week 4 and then an injection once every 12 weeks from then on. For patients weighing more than 100kg, the dose was 90mg (two injections) and was given at the same time as the lower dose (i.e. week 0, week 4, and then every 12 weeks from then on). The clinical and demographic characteristics of the patients were described and also PASI, DLQI and PDI scores were investigated at week 0, 4, 16, 26, and 28. At the end of 26 weeks the PASI score was evaluated due to flare up of psoriasis two weeks before previous injections.

Psoriasis Disability Index and Dermatology Life Quality Index

DLQI is a test consisting of 10 questions that are specific to skin diseases. The mean DLQI score (maximum 30) is ranged from 0 to 0.5 in the normal population. Compared to the normal population, DLQI has been shown to have a very high specificity in psoriasis.[8,9] PDI is the first survey-based validated scale defined in psoriasis that has been translated into more than 20 languages worldwide.[10,11] It is still popular and is used throughout the world to evaluate psoriasis.[12-14]

Metabolic syndrome

The metabolic syndrome was evaluated according to the national cholesterol education program's adult treatment panel III report criteria and effect of the metabolic syndrome on the UST treatment was investigated. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) report, five criteria for the diagnosis of metabolic syndrome have been identified. The presence of three out of five criteria was reported to be sufficient for the diagnosis of metabolic syndrome. These criteria include: abdominal obesity (waist circumference: >102 cm in men, >88 cm in women), hypertriglyceridemia (≥150 mg/dl), low HDL (<40 mg/dl in men, <50 mg/dl in women), hypertension (blood pressure ≥130/85 mmHg) and hyperglycemia (fasting blood glucose ≥110 mg/dl).[15,16] The study was approved by the local ethics and clinical research committee of the hospital (0037-372/2018).

Data were analyzed by using the SPSS 20.0 package program (SPSS Inc., Chicago, IL, USA) and statistical significance was determined at the 95% confidence interval and $p<0.05$. Mean±SD was provided for numerical variables as descriptive statistics, and numbers (%) were given for categorical variables. Odds ratio (OR) was calculated for the risk assessment. Mann-Whitney U test was used for data that were not normally distributed for continuous variables.

RESULTS

Five men and 4 women patients with plaque type psoriasis were included in this study.

Table 1: Demographic and clinical characteristics of patients receiving ustekinumab.

S. no.	Gender/ age	BMI	Previous biological treatment presence	The presence of Pa	Presence of Ms	PASI score (0/28th week)	PASI 75 response	DLQI (0/28 week)	Concomitant systemic treatment
1	M/50	39.44	IFX	None	Yes	41.1/3.9	Yes	7/0	MTX
2	F/63	28.76	None	None	None	40.4/14.4	None	4/1	None
3	F/44	27.34	IFX	None	None	21.0/9.2	None	6/6	None
4	M/55	28.36	ETC	None	None	59.0/6.3	Yes	9/6	ACT
5	M/20	21.55	None	Yes	None	48.3/1.0	Yes	15/0	None
6	M/40	25.35	None	Yes	None	25.3/0.0	Yes	24/0	None
7	F/49	31.60	ETC, IFX, ADA	Yes	Yes	40.0/17.6	None	9/21	LEF
8	M/48	24.78	IFX, ETC	Yes	None	33.0/10.4	None	16/5	None
9	F/34	33.62	IFX, ADA	Yes	Yes	24.8/0.0	Yes	27/0	None

ADA=adalimumab BMI=body mass index, PASI: psoriasis area and severity index, DLQI: dermatology life quality index, ETC=etanercept, IFX=infliximab, LEF=leflunamid, Ms=metabolic syndrome, MTX=methotrexate, Pa=psoriatic arthritis.

Table 2: Changes in psoriasis area and severity index score during ustekinumab treatment.

PASI score	Week 0	Week 4	Week 16	Week 26	Week 28
Mean	36.90	8.87	9.52	3.56	6.97
Median	40.00	8.80	6.60	2.00	6.30
SD	12.28	9.07	11.55	3.61	6.40
Minimum	21.00	0.00	0.60	0.00	0.00
Maximum	59.00	29.9	38.70	10.20	17.60

PASI: psoriasis area severity index.

Table 3: Changes in dermatology quality of life index and psoriasis disability index scores during ustekinumab treatment.

Variables	DLQI/PDI score				
Weeks	**Mean**	**Median**	**SD**	**Minimum**	**Maximum**
0	13.11/24.67	10.00/24.00	8.06/11.12	4/9	27/45
4	4.11/12.89	2.00/12.00	5.13/9.44	0/2	13/31
16	4.22/9.33	2.00/7.00	6.74/10.01	0/0	21/27
28	1.86/8.75	1.00/4.50	2.27/10.99	0/0	6/31

DLQI: dermatology quality of life index, PDI: psoriasis disability index.

Table 4: Psoriasis disability index, psoriasis area severity index, and dermatology quality of life index scores of patients with and without metabolic syndrome at the end of the 28th weeks.

Variables	Patients with metabolic syndrome (n=3)			Patients without metabolic syndrome (n=6)		
	PDI	**PASI**	**DLQI**	**PDI**	**PASI**	**DLQI**
Mean	16.50	7.16	8.33	6.17	6.89	2.17
Median	16.50	3.90	1.00	4.00	7.75	2.00
SD	20.51	9.24	14.43	7.28	5.60	2.31
Minimum	2.00	3.90	0.00	0.00	0.00	0.00
Maximum	31.00	17.60	25.00	19.00	14.40	6.00

DLQI: dermatology quality of life index, PASI: psoriasis area severity index, PDI: psoriasis disability index.

The mean age of the patients was 44.78±12.4 years. In addition, the mean body mass index value of the patients was 28.9±5.3 kg/m^2 (minimum 21.5, maximum 39.4) while the mean duration of disease was 24.67±10.1 years (minimum 12, maximum 45). Five patients had psoriatic arthritis associated with psoriasis and 3 patients had metabolic syndrome. One patient received acitretin with UST since the 16th week of treatment, while the other two patients received methotrexate and leflunomide with UST since the first week. At the end of week 28, the number of patients achieving PASI 75 was 5 (55%) and the other 4 patients achieved PASI 50 response (Table 1).

The mean PASI, DLQI and PDI scores of the patients receiving UST were recorded for each treatment session. The mean PASI scores of the patients at week 0, 4, 16, 26, and 28 were 36.98 ±12.28, 8.86± 9.06, 9.52±11.55, 3.55±3.61 and 6.98±6.40, respectively. In addition, the mean DLQI scores for 0, 4, 16 and 28 weeks were 13.11±8.06, 4.11±5.13, 4.22±6.741, 1.86±2.27, and the mean PDI scores were 24.67±11.12, 12.89±9.44 and, 9.33±10.01, 8.75±10.99, respectively (Figure 1, Table 2 and 3).

The mean PASI, DLQI and PDI scores of the patients with metabolic syndrome were higher than those without metabolic syndrome at the end of the 28th week. However, there was no statistically significant difference between these two groups in terms of mean PASI, DLQI and PDI scores (p=0.505, p=0.314, p=0.786) (Table 4).

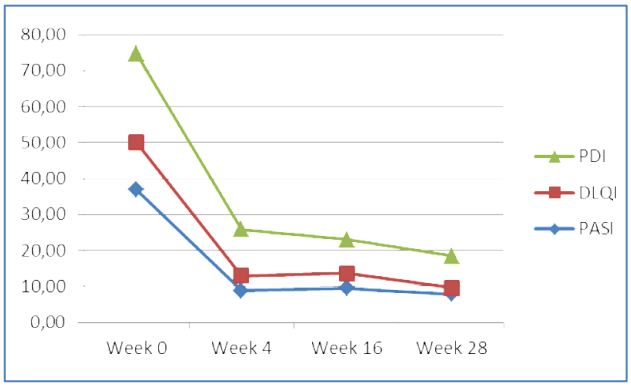

Figure 1: Changes in mean PDI, DLQI, and PASI values during 28 weeks of follow-up.

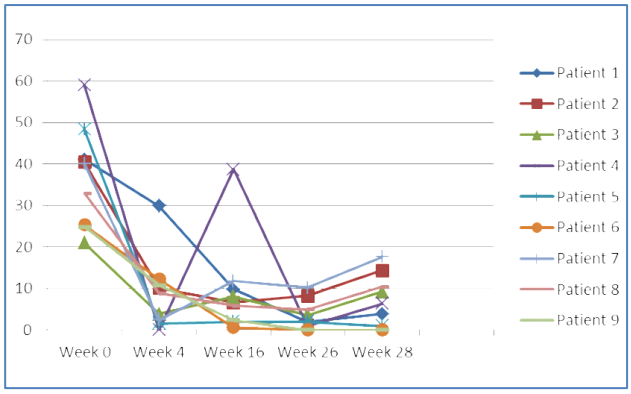

Figure 2: Changes in mean PASI scores during 28 weeks of follow-up in patients under ustekinumab treatment.

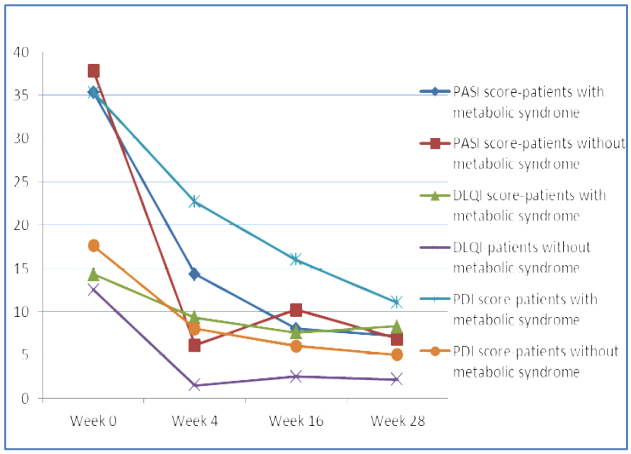

Figure 3: Changes in mean PASI, DLQI, and PDI scores during 28 weeks of follow-up in patients with and without metabolic syndrome.

DISCUSSION

Psoriasis is a chronic systemic autoimmune inflammatory disease that causes an increased turnover of skin cells. Psoriasis vulgaris represents its most common form, with a prevalence of 1-3% in the general population.[17,18] The pathogenesis of psoriasis was initially defined as increased expression of Th1 cytokines such as IL-2, IFN-γ and TNF-α in psoriatic lesions.[19] After IL-12 and IL-23 cytokines were shown to induce secretion of cytokines such as IL-2, 6, 17 and 22 by maturing Th1 and Th17 cells in the pathogenesis of psoriasis, IL-12/23 inhibitors were developed for treatment of the disease.[20,21] Ustekinumab is known as an anti-IL12/23 IgG1 kappa human monoclonal antibody, approved by the FDA in 2009 for the treatment of psoriasis.[5] Since its approval for the treatment of psoriasis, a number of clinical studies, which still preserve its popularity, have been conducted on the effectiveness and safety of UST. The most effective parameters that measure the efficacy of treatment in these studies are the DLQI score with the change in PASI score as in our study.[22,23]

In this study, clinical responses during periods of follow-up were maintained through week 28. In addition to PASI score, periodic DLQI and PDI scores of patients were also calculated. Although not statistically significant, interestingly, while the mean PASI score of the nine patients who were admitted to the clinic at 26 weeks (2.5 months after the last injection) was 3.55±3.61, it was increased as 6.98±6.40 within two weeks (3 months after the last injection) (Figure 2). In this regard, it can be considered that the treatment interval should be reduced in patients with resistance to the 3 month-interval UST treatment. Further studies such as randomized controlled trials are required to elucidate this issue.

In the present study, DLQI and PDI scores correlated with PASI score and the maximum response to UST treatment was observed at week 26 compared with previous weeks (Figure 1). In this context, it can be speculated that UST may have a cumulative effect. The PASI 75 response was obtained in 55% of patients and PASI 50 response was obtained in all patients. Three out of the four patients who did not achieve the PASI 75 response, did not respond to previous anti-TNF treatments. The failure of these patients to achieve the PASI 75 response can be explained in several ways. Patients with the HLA-Cw6 polymorphism have a higher level of response to UST. The differences in HLA-Cw6 polymorphism in these patients may explain this change in response.[24] However, it can be concluded that different pathways that trigger psoriasis may be at the forefront in these patients. In recent years, IL-17 has been found to play an active role in the pathogenesis of psoriasis. IL-17 was found to induce neutrophil chemoattractant chemokines and antimicrobial peptide expression, maintain chronic inflammation and induce psoriasis by IL-17A upregulating the keratinocyte chemokine CCL20.[25-27] In this context, biological agent therapies acting on the IL-17 pathway may be used in cases resistant to anti-TNF and UST treatments.[28]

Another finding in this study was the response to UST treatment in patients with metabolic syndrome. There are no sufficient studies on the relationship between response to biological agents and the presence of metabolic syndrome in psoriasis. The cytokine dysregulation of TNF-alpha, IL-6, and, IL-17 caused by Th-1 and Th17 in psoriasis, can induce insulin resistance and obesity by antagonizing the insulin signalling pathway, as well as altering the expression of adipokine and increasing proliferation of epidermal keratinocytes. In contrast, hyperinsulinemia in metabolic syndrome may also induce angiogenesis and chronic inflammation leading to the formation of psoriasis.[29-31] It has been reported that psoriasis will be more severe in patients with metabolic syndrome.[32] In this study, mean PASI, DLQI and PDI scores of the patients with metabolic syndrome were 7.16±9.7, 8.3±14.43, and 16.5±20.5, while for patients without metabolic syndrome these scores were 6.9±5.6, 2.2±2.3 and, 6.17±7.2, respectively at the end of the 28 weeks (Figure 3). In this regard, it can be speculated that

patients with psoriasis accompanying metabolic syndrome will have a lower response rate to UST treatment than those without metabolic syndrome. Optimal response from biological treatment can be achieved by overcoming obesity and insulin resistance. The main limitations of this study include a small sample size. This is a preliminary study, future studies with a larger number of patients will enable this subject to be examined in detail.

CONCLUSION

In conclusion, UST is an effective treatment option that can be used in patients with psoriasis who resistant to conventional and/or other biological treatments. In resistant cases, the routine treatment interval of 3 months for UST should be reduced. Lastly, patients with psoriasis accompanying metabolic syndrome may have a lower response rate to UST treatment than those without metabolic syndrome. This issue should be clarified by future studies that include large samples.

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