Halobetasol propionate lotion 0.05% in patients 12 to 16 years 11 months of age with plaque psoriasis: Results of an open-label study evaluating adrenal suppression potential

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Background: The effects of halobetasol propionate (HBP) lotion 0.05% on the hypothalamic-pituitary-adrenal (HPA) axis have not been previously evaluated in adolescents.

Objective: To examine the effect of HBP on HPA axis suppression in patients aged <17 years with plaque psoriasis.

Methods: In this phase 4, open-label, multicenter study, patients aged 12 to 16 years 11 months with stable plaque psoriasis covering ≥10% of their body surface area were enrolled. The patients applied an HBP lotion twice daily for up to 2 weeks. The cosyntropin stimulation test was used to determine cortisol levels at the time of screening and at the end of the study to evaluate HPA axis response. The additional endpoints included adverse events, disease severity (measured using Investigator Global Assessment score), and percent body surface area affected.

Results: Sixteen patients were enrolled and included in the safety population; 14 were included in the evaluable population. One patient exhibited an abnormal HPA axis response (16.2 μg/dL) at the end of the study; the response returned to normal at the 6-month follow-up visit. By the end of the study, the Investigator Global Assessment score improved by ≥1 point in most patients; moreover, the percent body surface area affected decreased from 11.5% to 2.8%. One mild adverse event was possibly related to the HBP lotion; however, it resolved and did not cause study discontinuation.

Limitations: Small sample size.

Conclusion: The HBP lotion 0.05% appeared efficacious and well tolerated in patients as young as 12 years old. (JAAD Int 2022;6:13-9.)

Key words: adolescent; adrenal suppression; corticosteroids; halobetasol propionate; pharmacology; psoriasis.

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INTRODUCTION

Psoriasis is a common chronic, inflammatory dermatologic disorder that can result in disease sequelae and decreased quality of life.[1] In approximately 33% of patients, psoriasis begins during childhood, with plaque psoriasis as the most common type of psoriasis in children.[2-4] The negative impact of psoriasis on the quality of life and psychological well-being has been established, and these effects may be cumulative.[5,6] Therefore, early and effective management of plaque psoriasis is particularly crucial in the adolescent population.

Topical therapies, including topical corticosteroids, have been used to manage plaque psoriasis for >50 years.[7] Halobetasol propionate (HBP) lotion 0.05% is a high-potency corticosteroid approved for the topical treatment of plaque psoriasis in adults and children ≥12 years old.[8] The extent of the absorption of a topical corticosteroid depends on a number of factors, such as structure and concentration, vehicle used, duration and frequency of application, occlusion, condition of the skin, and individual variation.

Although generally effective, an important potential adverse systemic effect of all topical corticosteroids, especially high-potency corticosteroids, is reversible hypothalamic-pituitary-adrenal (HPA) axis suppression.[7] HPA axis suppression is rarely reported and often characterized by the misuse of topical steroids.[7] Excess and prolonged absorption of corticosteroids may cause disruption of HPA axis homeostasis through the suppression of hypothalamic corticotrophin-releasing hormone, a major regulator of the HPA axis, and the suppression of pituitary adrenocorticotropic hormone, which directly affects adrenal gland cortisol production.[7,9] Reduction of HPA axis function is often not associated with clinical symptoms.[7]

The suppression of cortisol production can be determined based on an examination of plasma or serum cortisol concentrations before, during, and after the application of a topical corticosteroid. The gold standard to assess the HPA axis is the measurement of cortisol levels after stimulating the adrenal cortex with cosyntropin; this helps in testing the ability of the HPA axis to act as a negative feedback mechanism.[7,10,11] Early and accurate detection of HPA axis suppression is crucial because the consequences of this suppression include an insufficient bodily response to significant stress (illness, accident, surgery, etc), adrenal crisis, coma, or death.[12,13]

The potential of HBP lotion to suppress the HPA axis in patients <18 years of age has not yet been investigated. The objective of this study was to determine the adrenal suppression potential and pharmacokinetic (PK) properties of HBP lotion 0.05% (Ultravate Lotion; Sun Pharmaceuticals Industries Inc) in patients 12 years to 16 years 11 months of age with stable plaque psoriasis.

CAPSULE SUMMARY

- The safety of halobetasol propionate lotion 0.05% with respect to adrenal suppression and systemic exposure has been established in adults with plaque psoriasis; this study demonstrates similar findings in adolescents.
- This study supports the use of halobetasol propionate lotion 0.05% in patients ≥12 years old with stable plaque psoriasis.

METHODS

Study design

This phase 4, open-label, multicenter study was conducted at 5 centers in the United States (NCT03212963). All patients provided written informed consent and were accompanied by a parent or legal guardian at the time of consent or consent signing. The parent or legal guardian provided informed consent for the patient.

In this study, adolescent patients aged 12 years to 16 years 11 months with clinically diagnosed stable plaque psoriasis covering ≥10% of the body surface area (BSA; excluding the face, scalp, groin, axillae, and other intertriginous areas) and an Investigator Global Assessment (IGA) score of ≥3 (moderate) were enrolled. The key exclusion criteria included nonplaque forms of psoriasis, comorbidities that potentially affect adrenal axis function (eg, Addison disease and Cushing syndrome), and the use of phototherapy (including laser), photochemotherapy, or systemic or topical psoriasis therapy 30 days prior to treatment initiation or an abnormal HPA axis response at the time of screening (a poststimulation serum cortisol level of ≤18 μg/dL).

The patients applied a maximum of 50 g weekly of the HBP lotion 0.05% to all identified plaque psoriasis sites twice daily (approximately 12 hours apart) for up to 2 weeks or until the psoriasis sites cleared.

Study endpoints

The primary endpoint of this study was safety with the use of the HBP lotion 0.05%. The safety endpoints included HPA axis response to cosyntropin stimulation and trough HBP concentrations in the plasma. Adverse events (AEs) and local skin reactions (LSRs) associated with topical corticosteroids

Abbreviations used:

AE: adverse event
BSA: body surface area
CST: cosyntropin stimulation test
EOS: end of study
HBP: halobetasol propionate
HPA: hypothalamic-pituitary-adrenal
IGA: Investigator Global Assessment
LSR: local skin reaction
max: Maximum
min: Minimum
PK: pharmacokinetics

(telangiectasia, skin atrophy, burning or stinging, and folliculitis) were also scored and recorded for determining their severity at all postscreening visits. The secondary efficacy endpoints included the IGA score to assess disease severity and percent BSA treated and affected with the disease over the course of the study.

Assessments

Safety. A screening cosyntropin stimulation test (CST) was performed at each patient's first visit (screening) between 7:00 AM and 9:00 AM to determine the HPA axis response and confirm normal adrenal function prior to beginning the treatment phase of the study. If the patient had an abnormal HPA axis response, they were withdrawn from the study. To assess adrenal function at the end of the study (EOS), another CST was performed within 1 hour of the screening CST and ≥8 hours after applying a dose of the HBP lotion 0.05%. A patient exhibited adrenal suppression if the EOS CST resulted in an abnormal HBP axis response. Patients with adrenal suppression returned at least every 4 weeks for follow-up until the HPA axis response returned to normal.

AEs were reported during the study and coded using the Medical Dictionary for Regulatory Activities, v20.0. They were recorded as mild, moderate, or severe, and the relationship between an AE and the test article was classified as definitely related, probably related, possibly related, unlikely related, or not related. Telangiectasia, skin atrophy, burning or stinging, and folliculitis LSRs were recorded and graded by severity as mild, moderate, or severe.

Pharmacokinetics. At the time of screening, blood was drawn from all eligible patients to determine the baseline HBP concentration in the plasma. Additional blood samples were collected from the patients on days 8 and 15 (unless the disease was cured on day 8) to determine the trough HBP plasma concentrations. The blood collections were performed immediately prior to lotion application and approximately 12 hours after the previous dose. On day 15, a PK sample was obtained immediately prior to the CST.

Efficacy. The IGA score was assessed at the time of screening, at the baseline, on day 8, and on day 15 or at EOS. Each assessment was treated as a standalone assessment, and the investigators were instructed not to refer to previous assessments. The IGA score (ranging from 0 to 4 on a 5-point scale, with 0 indicating clear and 4 indicating severe) was used to evaluate the overall severity of a patient's plaque psoriasis based on 3 individual characteristics: scaling, erythema, and plaque elevation (Table I).

The percent BSA affected with plaque psoriasis was estimated at the baseline, on day 8, and on day 15 or at EOS. Additionally, the percent BSA treated with the HBP lotion 0.05% was estimated at the baseline and on day 8.

Statistical analyses

The safety population (n = 16) included all patients who received ≥1 dose of the HBP lotion 0.05%. The evaluable population (n = 14) included all patients in the safety population who also met the following criteria: both screening and EOS CSTs conducted between 7:00 AM and 9:00 AM, EOS CST conducted within 1 hour of the screening CST, applied ≥80% but ≤120% of expected applications with the final dose applied no more than 14 hours before the start of the EOS CST, no use of medications that may interfere with HPA axis function, and no other significant protocol deviations. Two patients did not meet the criteria for the evaluable population because the EOS CST was performed 6 days after their last dose. The 2 patients excluded from the evaluable population were also excluded from the PK population (n = 14).

Frequency counts and percentages were reported for all categorical data; mean, median, SD, minimum, and maximum were reported for continuous variables. The proportion of patients with adrenal suppression was presented along with 95% CIs. The changes in the observed serum cortisol levels after stimulation at the time of screening, at EOS, and at follow-up visits, if applicable, were also summarized. The morning trough concentrations of HBP in the plasma at the time of screening, on day 8, and on day 15 or at EOS were summarized using geometric mean, coefficient of variation, mean, median, SD, minimum, and maximum.

Frequency distributions of the observed IGA severity scores and changed IGA severity scores from the baseline were presented for each

Table I. Investigator's global assessment grading scale

Score	Grade	Assessment	Description
0	Clear		
		Scaling	No evidence of scaling.
		Erythema	No evidence of erythema (except possible residual coloration).
		Plaque elevation	No evidence of plaque elevation above normal skin level.
1	Almost clear		
		Scaling	No more than a limited amount of very fine scales partially covers some of the plaques.
		Erythema	No more than faint-red coloration.
		Plaque elevation	No more than very slight elevation above normal skin level, easier felt than seen.
2	Mild		
		Scaling	No more than mainly fine scales; some plaques are partially covered.
		Erythema	No more than light-red coloration.
		Plaque elevation	No more than a slight but definite elevation above normal skin level, typically with indistinct or sloped edges on some of the plaques.
3	Moderate		
		Scaling	No more than somewhat coarser scales predominate; most plaques are partially covered.
		Erythema	No more than moderate-red coloration.
		Plaque elevation	No more than a moderate elevation, with rounded or sloped edges on most of the plaques.
4	Severe		
		Scaling	Coarse, thick tenacious scales predominate; virtually all or all plaques are covered; rough surface.
		Erythema	Dusky to deep-red coloration.
		Plaque elevation	Marked to very-marked elevation, with hard to very-hard sharp edges on virtually all or all the plaques.

visit. Descriptive statistics were provided for the observed values and changes from the baseline with respect to both the percent BSA affected and treated for the evaluable and PK populations. All statistical analyses and summaries were prepared using SAS.

RESULTS

Patient characteristics and baseline demographics

Overall, 19 patients were screened; of them, 16 consecutive eligible patients were enrolled, who completed the study. The 3 screen failures were due to abnormal HPA axis responses. The mean (SD) age was 14.1 (1.51) years, and a majority (62.5%) of the patients were boys (Table II).

Table II. Demographic and baseline characteristics*

Characteristics	0.05% HBP
Sex, male, n (%)	10 (62.5)
Age, mean (SD), y	14.1 (1.5)
Median (min-max)	13.6 (12.5-16.9)
Race, White, n (%)	16 (100)
Ethnicity, Hispanic or Latino, n (%)	16 (100)
IGA score, n (%)	
Clear (0)	0
Almost clear (1)	0
Mild (2)	0
Moderate (3)	14 (87.5)
Severe (4)	2 (12.5)
Percent BSA affected, mean (SD)†	11.5 (1.3)
Percent BSA treated, mean (SD)†	11.1 (1.1)

BSA, Body surface area; *HBP*, halobetasol propionate; *IGA*, Investigator Global Assessment; *max*, maximum; *min*, minimum.
*Data presented for safety population (n = 16) unless otherwise indicated.
†Data presented for evaluable population (n = 14).

Safety

One patient (7.1%; 95% CI: 0.2-33.9) in the evaluable population had an abnormal HPA axis response on day 15 or at EOS (16.2 μg/dL). This was also the patient in the safety population (6.3%; 95% CI: 0.2-30.2) who experienced an abnormal response in the EOS CST. The patient's post-CST cortisol levels were monitored at the follow-up visits, which returned to normal approximately 6 months after day 15 or EOS.

The plasma trough concentration of HBP was below the quantifiable limit (0.02 ng/mL) at all time

Table III. Summary of local skin reactions*†‡

	None	Mild	Moderate	Severe
Predose telangiectasia				
Baseline	11 (68.8)	4 (25.0)	1 (6.3)	0
Day 8	11 (68.8)	5 (31.3)	0	0
Day 15 or EOS	13 (81.3)	3 (18.8)	0	0
Predose burning or stinging				
Baseline	4 (25.0)	11 (68.8)	1 (6.3)	0
Day 8	9 (56.3)	7 (43.8)	0	0
Day 15 or EOS	15 (93.8)	1 (6.3)	0	0
Postdose burning or stinging				
Baseline	6 (37.5)	10 (62.5)	0	0
Day 8	13 (81.3)	3 (18.8)	0	0

EOS, End of study.
*Data presented as n (%).
†Data presented for safety population (n = 16).
‡Skin atrophy and folliculitis are not shown because they were not reported during the study.

points for all patients, except 1, who had a slightly elevated HBP trough concentration of 0.0282 ng/mL on day 15 or at EOS.

Overall, there were no serious treatment-emergent AEs. The only AE was an abnormal adrenocorticotropic hormone stimulation test result at EOS, experienced by 1 (6.3%) patient, which was deemed possibly related to the study medication. The AE was mild; however, it resolved, and the patient continued in the study. At the baseline, prior to the application of the HBP lotion 0.05%, 1 (6.3%) patient reported a moderate telangiectasia LSR and 1 (6.3%) patient reported a moderate burning or stinging LSR. All other reported cases of telangiectasia and burning or stinging LSRs were mild (Table III). By EOS, all the patients either improved or remained the same as those at the baseline. The AEs and/or cases of telangiectasia and burning or stinging LSRs (whichever applies) either improved or remained the same as those at the baseline (Table III). There were no severe LSRs; folliculitis and skin atrophy were absent for all the patients at all visits.

Efficacy

At the baseline, 12 patients in the evaluable population had moderate plaque psoriasis (IGA grade 3) and 2 patients had severe plaque psoriasis (IGA grade 4). On day 15 or at EOS, 2 (14.3%) patients had IGA grade 3, whereas the remaining patients had grade 2, 1, or 0 (Fig 1). Thirteen (92.9%) patients had ≥1-point improvement in their IGA score. At the baseline, the mean (range) percent BSA affected was 11.5% (10%-14%), which decreased to 2.8% (0%-10%) by EOS (Fig 2). The mean (SD) change in the percent BSA affected from the baseline to EOS was −8.7% (3.2). Similarly, at the baseline, the mean (range) percent BSA treated with the HBP lotion 0.05% was 11.1% (10%-14%), which decreased to 7.1% (3%-10%) by day 8 (Fig 2). The mean (SD) change in the percent BSA treated with the HBP lotion 0.05% from the baseline to day 8 was −4.1% (2.0).

DISCUSSION

This study investigated the adrenal suppression potential and PK properties of a lotion formulation of 0.05% HBP applied twice daily in patients of 12 years to 16 years 11 months of age with stable plaque psoriasis. Minimal adrenal suppressive effects were observed, suggesting the potential safety of HBP lotion 0.05% under maximal-use conditions in adolescent populations.

Systemic absorption is a common concern following repeated application of topical corticosteroids, especially high-potency corticosteroids like HBP lotion 0.05%.[7] With prolonged use of corticosteroids, the suppression of the HPA axis and adrenal insufficiency due to adrenal gland atrophy may occur.[7] HPA axis suppression is one of the most important potential adverse effects of corticosteroids. If HPA axis suppression is prolonged, the adrenal glands may undergo atrophy, which can lead to dysfunction of the HPA axis. Furthermore, if one is unaware that HPA axis suppression is present, more serious consequences may arise, such as adrenal crisis, coma, or death.[12] HPA axis suppression following the use of topical steroids in patients with psoriasis has been investigated in adults and occurs relatively rarely, although conflicting results have been reported; however, data on its long-term treatment effects and large treatment areas are lacking.[7,14] Additionally, the reduction of HPA axis function is reversible and not usually associated with clinical symptoms in adults.[7,14] However, adolescent patients may be more susceptible because of higher ratios of skin surface to body mass than adults.[15] This study found that the HBP lotion 0.05% was well tolerated by adolescent patients, as evidenced by the fact that only 1 patient demonstrated abnormal HPA axis function, which returned to normal approximately 6 months after the study ended. Notably, this patient demonstrated laboratory evidence of HPA axis suppression, but the suppression did not present clinically (ie, no notable signs or symptoms indicative of adrenal suppression). Further research may consider identifying factors in adolescent patients associated with higher risk of HPA axis suppression to identify at-risk patients and allow for patient-specific treatment plans and additional monitoring for axis suppression, as needed.

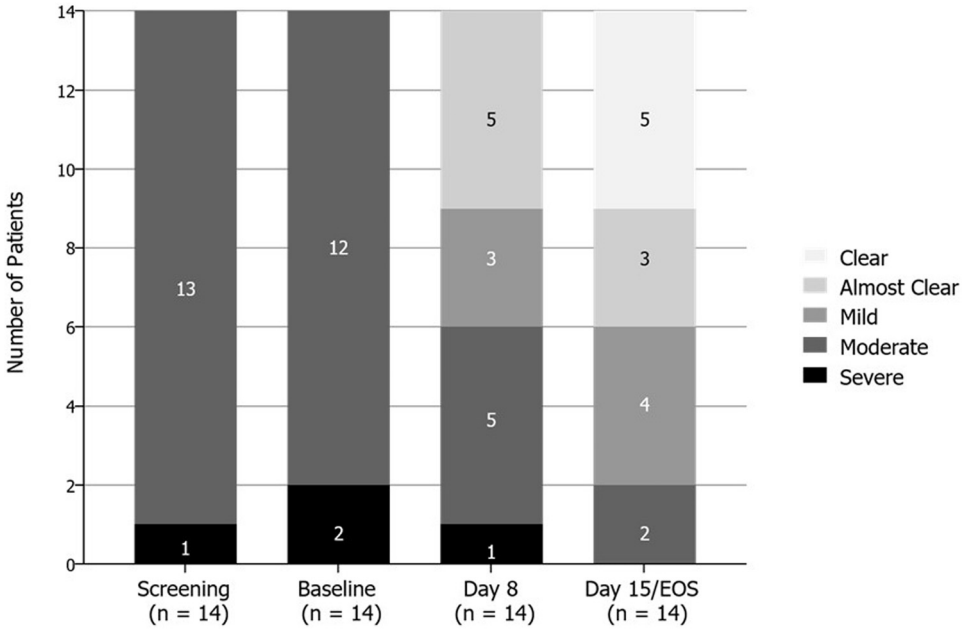

Fig 1. Plaque psoriasis. Investigator Global Assessment scores at each study visit. Disease severity was assessed on a 5-point scale from 0 to 4, with 0 indicating clear and 4 indicating severe. The data are presented from the evaluable population (n = 14). *EOS*, End of study.

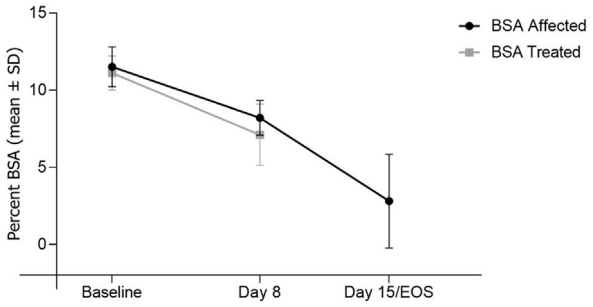

Fig 2. Plaque psoriasis. Percent body surface area affected and treated evaluated at each study visit. The data are presented from the evaluable population (n = 14). *BSA*, Body surface area; *EOS*, end of study.

The efficacy results of this study are comparable with those of published studies on potent topical corticosteroids used for the treatment of plaque psoriasis in adults. Topical formulations of HBP achieve treatment success, reduce psoriasis signs at target lesions, and improve BSA following a 2-week-daily treatment regimen.[16,17] In a randomized, double-blind, phase 2 study, 34% of adult patients using HBP lotion 0.05% for 2 weeks achieved a ≥2-grade improvement in baseline IGA score and were clear or almost clear at EOS, compared with only 3.3% of patients in the vehicle group.[16] In this study, all the patients, except 1, had a ≥1-point improvement in their IGA score, whereas 8 (57.1%) patients were considered cured or almost cured at EOS. Additionally, both the percent BSA affected with plaque psoriasis and percent BSA treated with the HBP lotion 0.05% decreased over the course of the study.

The safety profile, combined with the clear improvement in plaque psoriasis, in this study may support the use of HBP lotion 0.05% in the management of moderate-to-severe plaque psoriasis in adolescent populations. Effective therapies that minimize serious safety risks are especially important in this population because children with psoriasis may require treatment into adulthood. Systemic absorption of topical steroids depends on a number of factors, such as anatomic site and extent of the disease (% BSA affected).[7,15] Therefore, further research on the safety of HBP lotion 0.05% in patients 12 years to 16 years 11 months of age should be conducted in larger and more diverse patient populations to continue to understand the risk-benefit profile of HBP lotion in this population.

The limitations of this study include the small sample size and lack of a control group. Because HPA axis suppression is known to occur relatively rarely, larger studies are needed to better detect the rate of safety events among adolescent patients. Additionally, because this study investigated the use of HBP lotion 0.05% over 2 weeks, the results should not be applied to longer treatment plans.

Lastly, the study population was predominately Hispanic or Latino, and study findings are specific to the Fitzpatrick skin type of the study group. Care should be taken when applying these study findings to other Fitzpatrick skin types.

CONCLUSIONS

The HBP lotion 0.05% was locally well tolerated, showed minimal adrenal suppressive effects, and was efficacious in patients aged as young as 12 years. Overall, this study may support the use of HBP lotion 0.05% in children aged 12 years to 16 years 11 months with stable plaque psoriasis. Larger studies are needed to further establish the safety profile of HBP lotion in adolescent patients.

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Conflicts of interest

Dr Laquer has served on advisory boards for Almirall, Celgene, LEO Pharmaceuticals, Novartis, and Pfizer. Author Nguyen has served on advisory boards and as a consultant for Celgene; Foamix; IntraDerm Pharmaceuticals; LEO Pharmaceuticals; Mayne; Novartis; Pfizer; Sanofi Regeneron; and Sun Pharmaceutical Industries, Inc; as a speaker for Amgen; Celgene; Eli Lilly; Encore Pharmaceuticals; Janssen; LEO Pharmaceuticals; Mayne; Novartis; Sun Pharmaceutical Industries, Inc; and UCB. Dr Squittieri is an employee of Sun Pharmaceutical Industries, Inc. Dr Nguyen has served as a consultant for AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Corrona, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi Regeneron, and UCB; as an investigator for AbbVie, Amgen, Bristol-Myers Squibb, Biogen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, and Sanofi Regeneron; and as a speaker for AbbVie; Almirall; Amgen; Celgene; Eli Lilly; Novartis; Pfizer; Sanofi Regeneron; and Sun Pharmaceutical Industries, Inc.

REFERENCES

1. Frantz T, Wright EG, Balogh EA, Cline A, Adler-Neal AL, Feldman SR. Topical and oral therapies for childhood atopic dermatitis and plaque psoriasis. *Children (Basel)*. 2019;6(11):125.
2. Stefanaki C, Lagogianni E, Kontochristopoulos G, et al. Psoriasis in children: a retrospective analysis. *J Eur Acad Dermatol Venereol*. 2011;25(4):417-421.
3. Paller AS, Singh R, Cloutier M, et al. Prevalence of psoriasis in children and adolescents in the United States: a claims-based analysis. *J Drugs Dermatol*. 2018;17(2):187-194.
4. Raychaudhuri S, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. *Pediatr Dermatol*. 2000;17(3):174-178.
5. Bilgic A, Bilgic Ö, Akış HK, Eskioğlu F, Kılıç EZ. Psychiatric symptoms and health-related quality of life in children and adolescents with psoriasis. *Pediatr Dermatol*. 2010;27(6):614-617.
6. Remröd C, Sjöström K, Svensson A. Psychological differences between early- and late-onset psoriasis: a study of personality traits, anxiety and depression in psoriasis. *Br J Dermatol*. 2013;169(2):344-350.
7. Castela E, Archier E, Devaux S, et al. Topical corticosteroids in plaque psoriasis: a systematic review of risk of adrenal axis suppression and skin atrophy. *J Eur Acad Dermatol Venereol*. 2012;26(suppl 3):47-51.
8. Ultravate (halobetasol propionate) lotion. Full Prescribing Information. NJ, USA: Sun Pharmaceutical Industries IC; 2020.
9. DeMorrow S. Role of the hypothalamic-pituitary-adrenal axis in health and disease. *Int J Mol Sci*. 2018;19(4):986.
10. Hamilton DD, Cotton BA. Cosyntropin as a diagnostic agent in the screening of patients for adrenocortical insufficiency. *Clin Pharmacol*. 2010;2:77-82.
11. Cortrosyn (cosyntropin) for Injection. Full Prescribing Information. CA, USA: Amphastar Pharmaceuticals IRC; 2010.
12. Smith RW, Downey K, Gordon M, et al. Prevalence of hypothalamic-pituitary-adrenal axis suppression in children treated for asthma with inhaled corticosteroid. *Paediatr Child Health*. 2012;17(5):e34-e39.
13. Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child*. 2002;87(6):457-461.
14. Weston WL, Fennessey PV, Morelli J, et al. Comparison of hypothalamus-pituitary-adrenal axis suppression from superpotent topical steroids by standard endocrine function testing and gas chromatographic mass spectrometry. *J Invest Dermatol*. 1988;90(4):532-535.
15. Thomas J, Parimalam K. Treating pediatric plaque psoriasis: challenges and solutions. *Pediatric Health Med Ther*. 2016;7:25-38.
16. Bhatia ND, Pariser DM, Kircik L, et al. Safety and efficacy of a halobetasol 0.01%/tazarotene 0.045% fixed combination lotion in the treatment of moderate-to-severe plaque psoriasis: a comparison with halobetasol propionate 0.05% cream. *J Clin Aesthet Dermatol*. 2018;11(11):15-19.
17. Kerdel FA, Draelos ZD, Tyring SK, Lin T, Pillai R. A phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical study to compare the safety and efficacy of a halobetasol propionate 0.01% lotion and halobetasol propionate 0.05% cream in the treatment of plaque psoriasis. *J Dermatolog Treat*. 2019;30(4):333-339.