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Is Apremilast 30mg Effective in Lowering DLGI Scores in Patients with Plaque Psoriasis in 16 Weeks of Therapy?

Hunter N. Dennard
Philadelphia College of Osteopathic Medicine

Is Apremilast 30mg effective in lowering DLQI scores in patients with plaque psoriasis in 16 weeks of therapy?

Hunter N. Dennard, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not "Is Apremilast 30 mg effective in lowering DLQI scores in patients with plaque psoriasis in 16 weeks of therapy?"

Study Design: Review of three randomized, blind, placebo-controlled clinical trials published between the years 2013 and 2016.

Data Sources: All studies were published in peer-reviewed journals that were located using PubMed database searches.

Outcome Measured: The DLQI is a 10-item questionnaire that assesses the impact of skin disease on health-related quality of life (HRQOL) over the previous week. Scores for each item range from 0 (not at all affected) to 3 (very much affected); total scores range from 0 to 30 and those >10 represent a very large impact on HRQOL. Patients answered questions regarding their physical discomfort and limitations in activities of daily living to psychosocial problems and emotional distress caused by the condition.

Results: All studies showed a statistical significance when comparing Apremilast 30mg BID to a placebo therapy. DLQI scores were decreased by 6.7 points in the study performed by Paul et al., 8.3 points with Reich et al. data, and lastly 4.4 points with the Strand et al. study. (P- values for all studies <0.05)

Conclusion: According to this EBM review Apremilast 30mg is effective in lowering DLQI scores in patients with plaque psoriasis in 16 weeks of therapy. Some studies showed more significant decreases in DLQI scores but overall a patient would experience a lower impact of skin disease on health-related quality of life.

Key Words: Apremilast, Plaque Psoriasis.

INTRODUCTION

Plaque psoriasis is a common chronic inflammatory skin disease that is characterized by well-demarcated, erythematous plaques with an overlying silver scale. Pruritis is the main symptom patients physically experience and varies from mild to severe.[1] Often the disease is asymptomatic, but other symptoms may include skin pain or Auspitz sign, which is pin-point bleeding when there is minor abrasion to a plaque.[1] Plaque psoriasis can affect patients in varying degrees of severity; some patients having minimal visible skin lesions while others experience a greater percentage of their body surface area being covered. Smaller areas of plaques often will coalesce into larger plaques causing increased physical and psychosocial discomfort.[1] Typically the scalp, lower back, trunk, and extremities are involved but the extensor surfaces of joints such as the elbows and knees have an increased predilection.[2] Psoriasis may not produce physical discomfort for all patients but it is associated with potentially antagonistic effects on mental health.[2] Patients are at increased risk for depression, anxiety, and suicidality when compared with the general population.[3] Due to these factors many patients elect to begin treatment to increase their overall quality of life and social interactions.

Although earlier concepts of the pathogenesis of psoriasis were more focused on keratinocyte hyperproliferation, dysregulation of the immune system is now recognized as the main cause of the disease.[1] The interactions between dendritic cells, T cells, keratinocytes, neutrophils, and the cytokines released from immune cells likely contribute to the initiation of the cutaneous skin inflammation that is characteristic of psoriasis.[4] There is also a genetic factor to consider, as approximately 40% of patients with psoriasis have a family history of the disease in a first-degree relative.[5] Other factors that play a role in the development of psoriasis include tobacco and alcohol use, certain medications, infections, and stress.[6]

Psoriasis is estimated to affect more than 8 million Americans and is one of the most common dermatologic and autoimmune conditions treated in the world.[2] There are approximately 150,000 cases of psoriasis that are diagnosed annually, which contributes to 3 million visits to healthcare facilities for treatments.[7] With treatments often requiring the use of biologic agents healthcare costs can be overwhelming to a patient. Biologics as a mainstay for treatment can have a mean annual cost of $53,183.50 for a patient paying out of pocket.[8] The total burden of psoriasis was recently estimated as $35.2 billion in the United States.[9]

There is currently no cure for psoriasis as it is considered a chronic condition. Therapies are targeted at reducing the appearance and size of lesions as well as any associated discomfort. Topical therapies are recommended in mild disease states and emphasis on keeping the skin moisturized is stressed.[2] These therapies include emollients, corticosteroids, Vitamin D analogs, calcitriol, tar shampoos, taxarotene, and calcineurin inhibitors.[6] When the disease is affecting a larger body surface area ultraviolet light therapy may be recommended but can cause a patient to be more at risk to develop a skin malignancy.[6] In severe cases systemic agents such as methotrexate, etanercept, infliximab, and adalimumab may be indicated.[6]

These agents mentioned can help control the extensiveness of psoriasis but can be associated with negative side effects, increased medical costs, delayed response to treatment, and poor patient satisfaction.[10] It is important to have a drug that is designed to directly target the formation of psoriasis and also achieve a higher level of patient satisfaction. Apremilast, a phosphodiesterase 4 inhibitor, is an oral agent for the treatment of moderate to severe plaque psoriasis.[10] Phosphodiesterase 4 inhibition reduces production of multiple cytokines involved in the pathogenesis of psoriasis.[11] This paper assesses the efficacy of Apremilast in improving a patient's quality of life in a 16 week period.

OBJECTIVE

The objective of this selective evidence based medicine (EBM) review is to determine whether or not "Is Apremilast 30 mg effective in lowering DLQI scores in patients with plaque psoriasis in 16 weeks of therapy?"

METHODS

In order to be considered and included, the population studied had to be patients 18 years of age or older clinically diagnosed with chronic plaque psoriasis for 6 months or longer. The study had to be a randomized controlled trial that included a treatment group taking Apremilast 30mg orally twice day (BID) and the control group receiving a placebo. Outcomes were measured using Dermatology Life Quality Index (DLQI) self-report questionnaire scores and their mean change from baseline at 16 weeks of treatment.

To find appropriate articles, keywords that were used included: "Apremilast"; "Plaque Psoriasis". Articles had to be in the English language and published in peer-reviewed journals. The author used the listed keywords to search online PubMed databases that addressed the objective of this review and used a patient centered outcome to measure the overall effect on a patient's quality of life. For an article to be considered it had to be a randomized, blinded, placebo-controlled trial using Apremilast as a treatment option. These articles had to be published within the last 10 years to ensure all data was up to date. If an article included patients under the age of 18 it would be rejected and excluded from the data. The specific demographics and characteristics for each individual study can be found in Table 1.

TABLE 1: DEMOGRAPHICS & CHARACTERISTICS OF INCLUDED STUDIES

Study	Type	# Pts.	Age (years)	Inclusion criteria	Exclusion Criteria	W/D	Interventions
Paul et al.[11] (2015)	RCT, double blinded, placebo controlled	411	45.3 ±13.1	Adults ≥18 years of age were eligible if diagnosed with chronic plaque psoriasis for ≥ 12 months. Patients had moderate-to-severe plaque psoriasis, defined as Psoriasis Area and Severity Index (PASI) score ≥ 12.	Clinically significant cardiac, endocrinological, pulmonary, neurological, psychiatric, hepatic, renal, hematological or immunological disease; other major uncontrolled disease. Prolonged sun or ultraviolet exposure. Biologic therapy within 12-24 weeks, conventional systemic treatments within 4 weeks, topical treatments for psoriasis within 2 weeks.	60	Regimen of Apremilast 30mg orally BID
Reich et al.[12] (2017)	RCT, double-blind, placebo-controlled study	167	46.0 ±13.6	Adults aged ≥18 years were eligible if they had chronic plaque psoriasis for ≥12 months (PASI score ≥12). No prior exposure to a biologic therapy for psoriasis or psoriatic arthritis.	Patients with prior failure of >3 systemic agents for treatment of psoriasis History of known demyelinating diseases such as multiple sclerosis or optic neuritis or history of or concurrent congestive heart failure, including medically controlled, asymptomatic congestive heart failure; other clinically significant or major uncontrolled disease	15	Regimen of Apremilast 30mg orally BID
Strand et al.[10] (2013)	RCT, blinded, placebo-controlled	176	44.1 ± 14.7	Adults ≥18 years of age with stable, chronic, moderate to severe plaque psoriasis (PASI ≥12 for ≥ 6 months) who were candidates for therapy.	Concomitant phototherapy and use of systemic biologic agents, use of topical agents except for Eucerin cream; low potency corticosteroids for facial, axillary, and groin lesions; and coal tar shampoo or salicylic acid preparations for scalp lesions.	LOCF used	Regimen of Apremilast 30mg orally BID

OUTCOMES MEASURED

The outcomes were measured using the Dermatology Life Quality Index (DLQI) which is a 10-item questionnaire that assesses the impact of skin disease on health-related quality of life (HRQOL) over the previous week. Questions range from physical discomfort and limitations in activities of daily living to psychosocial problems and emotional distress experienced by the patient. Scores for each item range from 0 (not at all affected) to 3 (very much affected); total scores range from 0 to 30 and those >10 represent a very large impact on HRQOL. [10,11,12] The mean change from the baseline score at the start of therapy was collected at week 16 as well as other time intervals.

RESULTS

The three studies selected compared the effectiveness of Apremilast 30mg twice a day to a placebo when treating adults with chronic plaque psoriasis. All studies used the DLQI questionnaire to evaluate if the treatment given caused an overall improvement and mean change from baseline over a set of timed intervals (Table 2). Each study also included a P-value to show the statistical significance of Apremilast versus a placebo (Table 3).

TABLE 2. DLQI MEAN CHANGE FROM BASELINE IN 16 WEEKS

	Study 1	Study 2	Study 3
DLQI Mean Change from Baseline ± SD with Apremilast 30mg	-6.7	-8.3±7.7	-4.4 ±5.1
DLQI Mean Change from Baseline ± SD with Placebo	-2.8	-3.8±5.6	−1.9 ± 5.2

TABLE 3. STATISTICAL SIGNIFICANCE OF INTERVENTION VS. PLACEBO

	Study 1	Study 2	Study 3
P- Value	P<0.001	P<0.0001	P≤0.005

**Statistical significance was considered to be a p-value <0.05*

The first study by Paul et al., was a phase III, randomized, double-blind, placebo-controlled study that monitored the efficacy and safety of Apremilast 30mg twice a day over 52 weeks compared to a placebo. The study included three time periods, week 16, week 32, and week 52, where patient data was collected. It specifically excluded patients who had used biologics within 12-24 weeks, conventional systemic treatments within 4 weeks, topical treatments for psoriasis within 2 weeks, and anyone with prolonged sun or ultraviolet exposure. Such factors could cause a patient to experience a decrease in DLQI scores that are unrelated to Apremilast treatment. Additional exclusion and inclusion criteria can be seen in Table 1. Apremilast showed significant improvement at week 16 of the study with 70.8% of the population that had a DLQI score >5 decreasing their DLQI score by 5 or more points (Table 4). The mean change from baseline reported by the study showed overall a 6.7 point decrease in DLQI scores in patients treated with Apremilast 30mg twice a day (Table 2). Within the 16-week period 60 of 411 patients discontinued treatment due to multiple factors (Table 5). Missing data was handled with last-observation-carried-forward (LOCF) methodology.

TABLE 4. DLQI RESPONSE (DECREASE OF ≥ 5 POINTS) IN 16 WEEKS

	Placebo (%)	Apremilast 30 mg (%)	P-Value
Study 1	42.9	70.8	<0.001
Study 2	41.7	65.1	0.0032

TABLE 5. PATIENTS COMPLIANCE WITH INTERVENTION IN STUDY 1

Discontinued due to:	Adverse event	Lack of efficacy	Withdrawn consent	Lost to follow-up	Protocol violation	Non-Compliant	Other	Total
Placebo Group (n=137)	8	2	7	6	1	0	1	25
Apremilast 30mg BID (N=274)	12	3	9	6	2	1	2	35

The second study by Reich et al., was a phase IIIb, randomized, double blind, placebo-controlled study that monitored the efficacy and safety of Apremilast 30mg twice a day and Etanercept 50mg once daily subcutaneous injection compared to a placebo. The trial included a placebo-controlled phase through 16 weeks with the 3 separate test groups as well as an Apremilast extension phase through 52 weeks. It specifically included patients who had previously had inadequate response, intolerance or contraindication to ≥1 conventional systemic agents for treatment of psoriasis, were candidates for phototherapy or systemic therapy, and had no prior exposure to a biologic therapy for psoriasis or psoriatic arthritis. Additional criteria can be seen in Table 1. Apremilast again showed significant improvement at week 16 of the study with 65.1% of the population that had a DLQI score >5 decreasing their DLQI score by 5 or more points (Table 4). The mean change from baseline reported by the study showed overall a 8.3 point decrease in DLQI scores in patients treated with Apremilast 30mg twice a day (Table 2). Within the 16-week period 15 of 167 patients discontinued treatment due to multiple factors (Table 6). Last observation carried forward (LOCF) methodology was used to impute missing efficacy measurements.

TABLE 6. PATIENTS COMPLIANCE WITH INTERVENTION IN STUDY 1

Discontinued due to:	Adverse event	Lack of efficacy	Withdrawn consent	Other	Total
Placebo Group (n=84)	2	4	1	2	9
Apremilast 30mg BID (N=83)	2	3	0	1	6

The third study by Strand et al., was a phase IIb, randomized, controlled study that looked at improvements in patient reported outcomes with Apremilast therapy. The study had four groups that were monitored through 16 weeks. Patients were randomly placed in groups receiving one of the following; placebo, Apremilast 10mg BID, Apremilast 20mg BID, Apremilast 30mg BID. All inclusion and exclusion criteria of the study can be found in Table 1.

The mean change from baseline reported by the study showed overall a 4.4 point decrease in DLQI scores in patients treated with Apremilast 30mg BID (Table 2). This particular study did not give data concerning the number of patients who did not complete a full 16 weeks of therapy. Last observation carried forward (LOCF) methodology was used to impute missing data.

DISCUSSION

The goal of this study was to determine if Apremilast 30mg could effectively lower DLQI scores in patients in 16 weeks of therapy. With the analyzation of the three studies 30mg Apremilast proved to decrease DLQI scores within the 16-week time frame.

Apremilast was approved by the FDA for treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy as well as psoriatic arthritis in March of 2014.[13] Apremilast is also recognized by the brand name Otezla and is an oral medication that can be taken without regards to food.[14] Contraindications are not listed on US labels but on Canadian labeling it is contraindicated in pregnancy and breast feeding.[13] Common side effects listed include GI upset such as diarrhea, nausea, and vomiting.[13] Neuropsychiatric effects include increased risk of depression and suicidal ideation.[13] Weight loss may also be a concerning side effect. Dosage reduction is also recommended in patients with a CrCl <30 mL/min.[13] With the listed contraindications and side effects a significant portion of patients with psoriasis may not find Apremilast to be worth the shown treatment efficacy. Especially concerning is that a patient already suffering from depression due to their skin appearance may be put at an increased risk of harming themselves. It is important to monitor a patient's weight, renal function, and mood fluctuations regularly during therapy.

Cost and availability to patients is one of the largest draw backs. There is no generic available to patients in the US and tablets cost approximately $65.66 per tablet.[13] Coverage by insurances varies and many require failed biologic therapy to get approval for the medication.[15]

Currently Otezla offers a zero dollar copay for select patient populations and healthcare providers may also fill out forms stating medical necessity to obtain coverage for their patients.[14]

There are multiple limitations noted throughout the studies. The use of LOCF assumes that the missing data after patient's withdrawal are the same as the last value observed for that patient. The consequence of this particular assumption is that it imputes data without giving subject variability and it also alters the true sample size. All three studies used this methodology when dealing with patients who discontinued therapy. Some studies allowed low-potency topical corticosteroids as background therapy for face, axilla and groin psoriasis lesions, coal tar shampoo and/or salicylic acid preparations for scalp lesions and non-medicated emollients for body lesions were also permitted. Patients also were not prohibited from receiving live vaccinations during some of the studies. There were also no protocol requirements to stop the study medication for an infection in all studies. Infection side effects could cause DLQI scores to fluctuate unrelated to study treatments. All of these listed factors could affect the validity of results.

CONCLUSION

According to this EBM review Apremilast 30mg is effective in lowering DLQI scores in patients with plaque psoriasis in 16 weeks of therapy. Some studies showed more significant decreases in DLQI scores, but overall a patient would experience a lower impact of skin disease on health-related quality of life. The three studies used tested large populations with patient demographics being very closely matched within comparison groups. These factors helped to increase the validity of the results.

For future research to improve from past studies, there should be consideration that social interactions are at their peak during teenage years to young adulthood. The mean age studied was approximately 45 years of age between the three studies. Additional studies should look to

include a younger database of patients. Also, with first line treatment of plaque psoriasis being topical therapies such as emollients, corticosteroids, and Vitamin D analogs, application would typically be twice a day if using monotherapy. It would be important to compare compliance in patients to see if an oral medication or topical medication, taken twice daily, is preferred by a patient.

To face the large cost for the drug in today's market it is important that future research is aimed to directly compare other therapies such as biologics to Apremilast. This research should aim to show that Apremilast is equally effective as well as safer for patient usage. Such future research is warranted to help Apremilast gain more formulary coverage for patients with commercial insurance.

REFERENCES

1. Epidemiology, clinical manifestations, and diagnosis of psoriasis - UpToDate. https://www-uptodate-com.ezproxy.pcom.edu/contents/epidemiology-clinical-manifestations-and-diagnosisofpsoriasis?search=psoriasis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2. Accessed December 10, 2018.

2. National Psoriasis Foundation – NPF Professional Fact Sheets. https://www.psoriasis.org/publications/patient-education/fact-sheets. Accessed October 9, 2018.

3. The Risk of Depression, Anxiety, and Suicidality in Patients With Psoriasis: A Population-Based Cohort Study | Anxiety Disorders | JAMA Dermatology | JAMA Network. https://jamanetwork.com/journals/jamadermatology/fullarticle/210088. Accessed October 9, 2018.

4. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med*. 2009;361(5):496-509. doi:10.1056/NEJMra0804595

5. Gladman DD, Anhorn KA, Schachter RK, Mervart H. HLA antigens in psoriatic arthritis. *J Rheumatol*. 1986;13(3):586-592.

6. Treatment of psoriasis in adults - UpToDate. https://www-uptodate-com.ezproxy.pcom.edu/contents/treatment-of-psoriasis-in-adults?search=plaque%20psorasis&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3. Accessed October 9, 2018.

7. Feldman SR, Goffe B, Rice G, et al. The Challenge of Managing Psoriasis: Unmet Medical Needs and Stakeholder Perspectives. *Am Health Drug Benefits*. 2016;9(9):504-513.

8. Feldman SR, Wu JJ, Rastogi S, Menges B, Lingohr-Smith M, Lin J. The budget impact of brodalumab for the treatment of moderate-to-severe plaque psoriasis on US commercial health plans. *J Med Econ*. 2018;21(5):537-541. doi:10.1080/13696998.2018.1431920

9. Vanderpuye-Orgle J, Zhao Y, Lu J, et al. Evaluating the economic burden of psoriasis in the United States. *J Am Acad Dermatol*. 2015;72(6):961-967.e5. doi:10.1016/j.jaad.2015.02.1099

10. Strand V, Fiorentino D, Hu C, Day RM, Stevens RM, Papp KA. Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: Results from a phase IIb randomized, controlled study. Health Qual Life Outcomes. 2013;11:82. doi: 10.1186/1477-7525-11-82 [doi].

11. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: A phase III, randomized controlled trial (ESTEEM 2). Br J Dermatol. 2015;173(6):1387-1399. doi: 10.1111/bjd.14164 [doi].

12. Reich K, Gooderham M, Green L, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a

phase IIIb, randomized, placebo-controlled trial (LIBERATE). J Eur Acad Dermatol Venereol. 2017;31(3):507-517. doi: 10.1111/jdv.14015 [doi].

13. Lexicomp Online. http://online.lexi.com.ezproxy.pcom.edu:2048/lco/action/doc/retrieve/docid/patch_f/5070024. Accessed December 9, 2018.

14. Explore the Co-pay and Patient Support for Otezla | Otezla® (apremilast) Healthcare Professional Site. OtezlaPro 4.0. https://www.otezlapro.com/resources/co-pay/. Accessed December 9, 2018.

15. Formulary and Health Insurance Coverage Information for Otezla | Otezla® (apremilast) Healthcare Professional Site. OtezlaPro 4.0. https://www.otezlapro.com/resources/formulary-coverage/. Accessed December 9, 2018.